ISSN 0003-2999
vol. 60, no. 1 January 1981

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Anesthesia and Analgesia

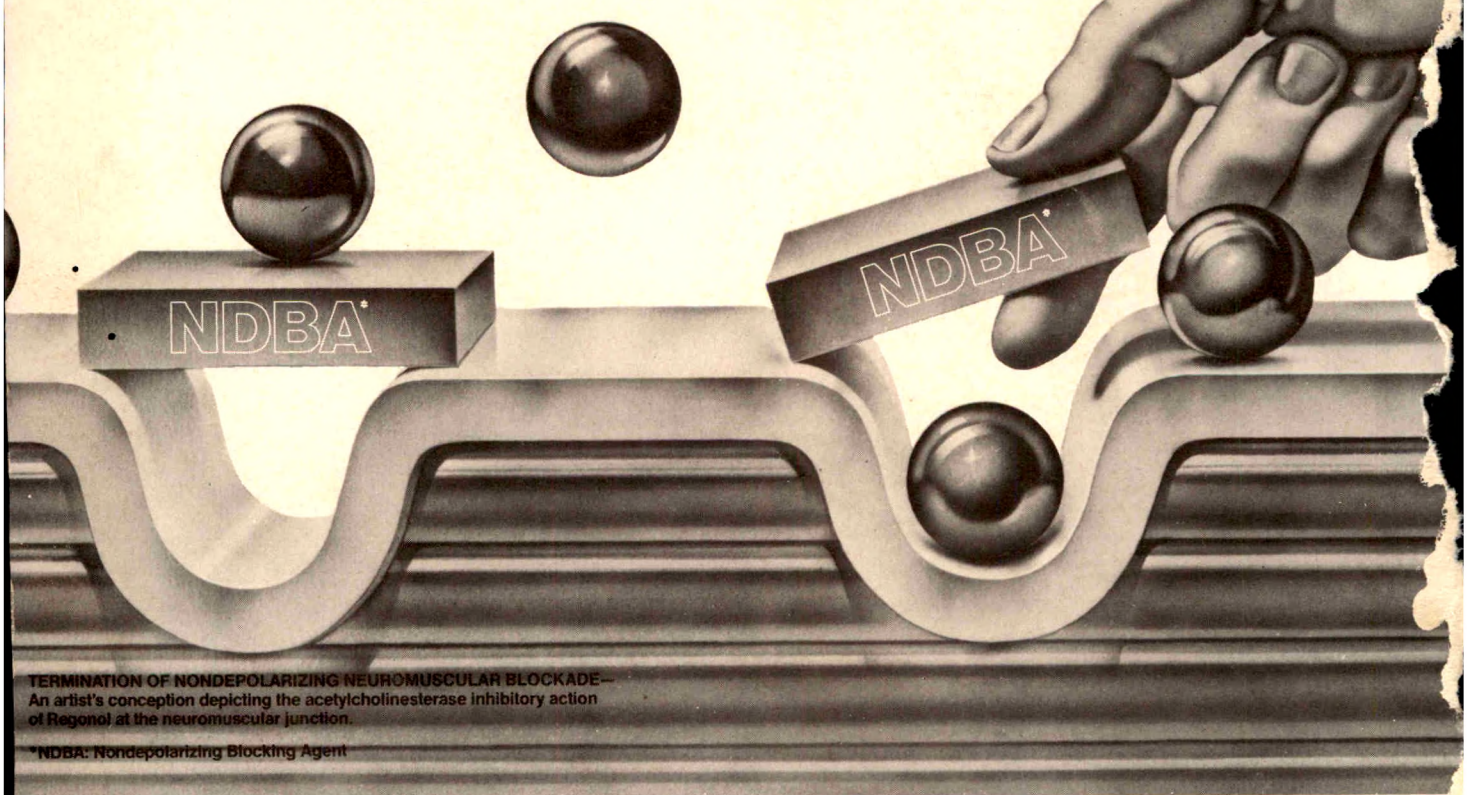
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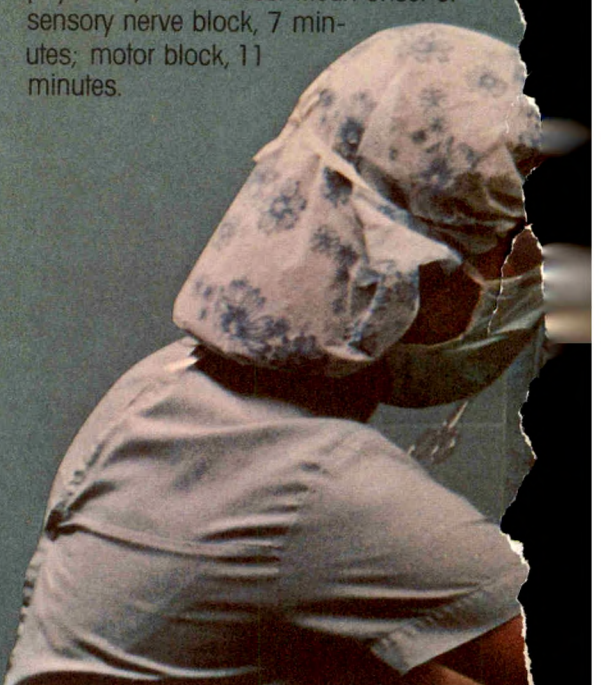
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ge in Pregnancy: Safe use of chloroprocaine has not been established with respect to adverse effects upon fetal development. This fact should be carefully considered before administering the drug to women of child-bearing potential, particularly during early pregnancy.

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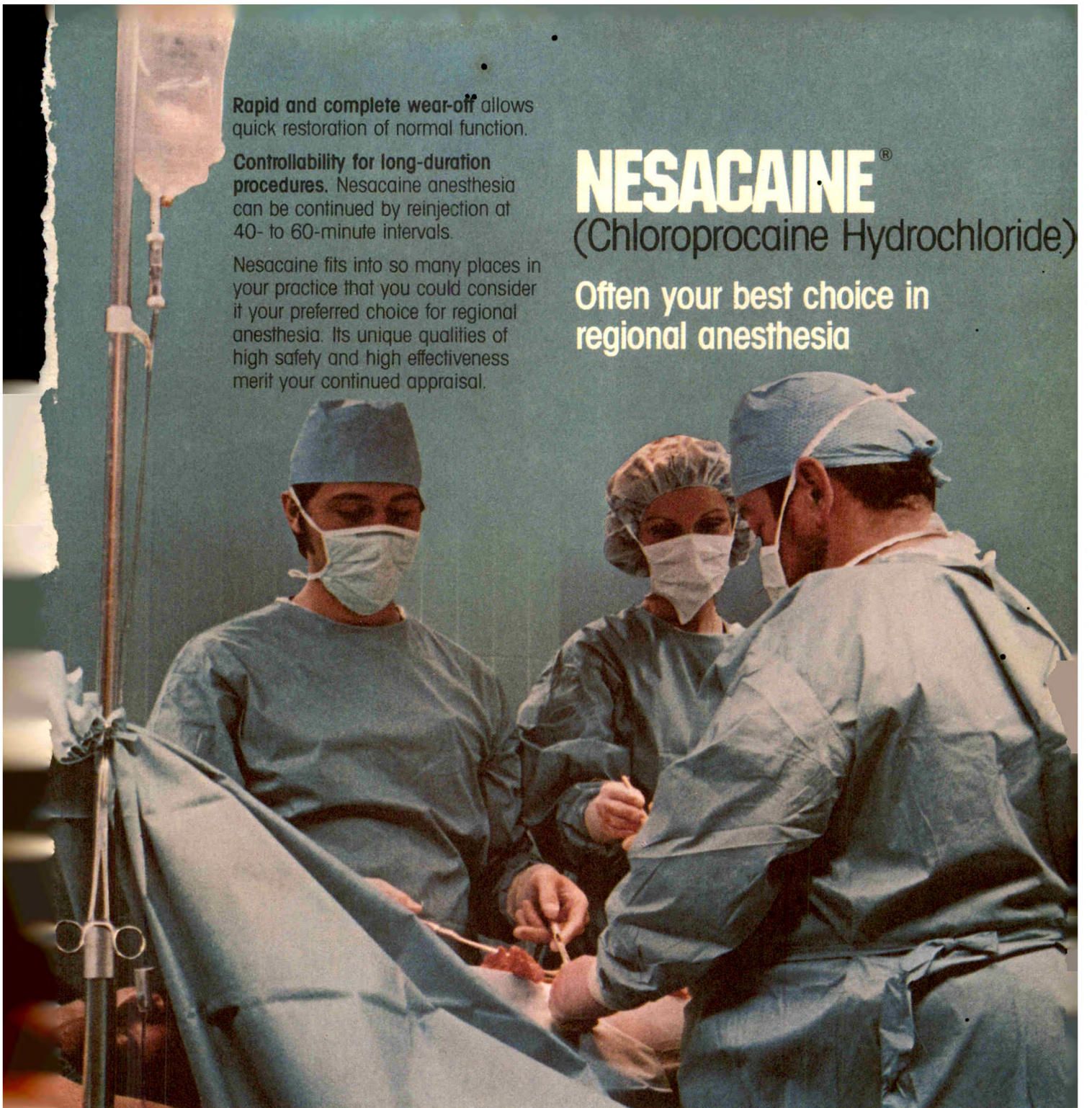
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REFERENCES:

1. Bonica JJ (ed): Obstetric Analgesia and Anesthesia. Berlin, Heidelberg, Springer-Verlag, 1972, pp 19, 51-52.
2. Nesacaine® (chloroprocaine hydrochloride) in obstetrical and surgical regional anesthesia, a Symposium, New York, KPR Infor/Media Corp, 1977, pp 12-27.
3. Ansbro FP, Blundell AE, Furlong RE, et al: Chloroprocaine (Nesacaine): Its relative nontoxicity as demonstrated by epidu anesthesia. Arch Surg 78:75-78, 1959.
4. Foldes FF: The management of pain in ambulatory patients. M Science Donat 7:26-37, 1969. (Proceedings of Symposium Pain, Amsterdam, March 1, 1969.)
5. Zsigmond EK, Kothary SP: 2-Chloroprocaine: Clinical pharmacology, pharmacokinetics and its safety in regional anesthesia. Presented as a scientific exhibit at the Internationa Anesthesia Research Society, Hollywood, Fla, March 11-15,

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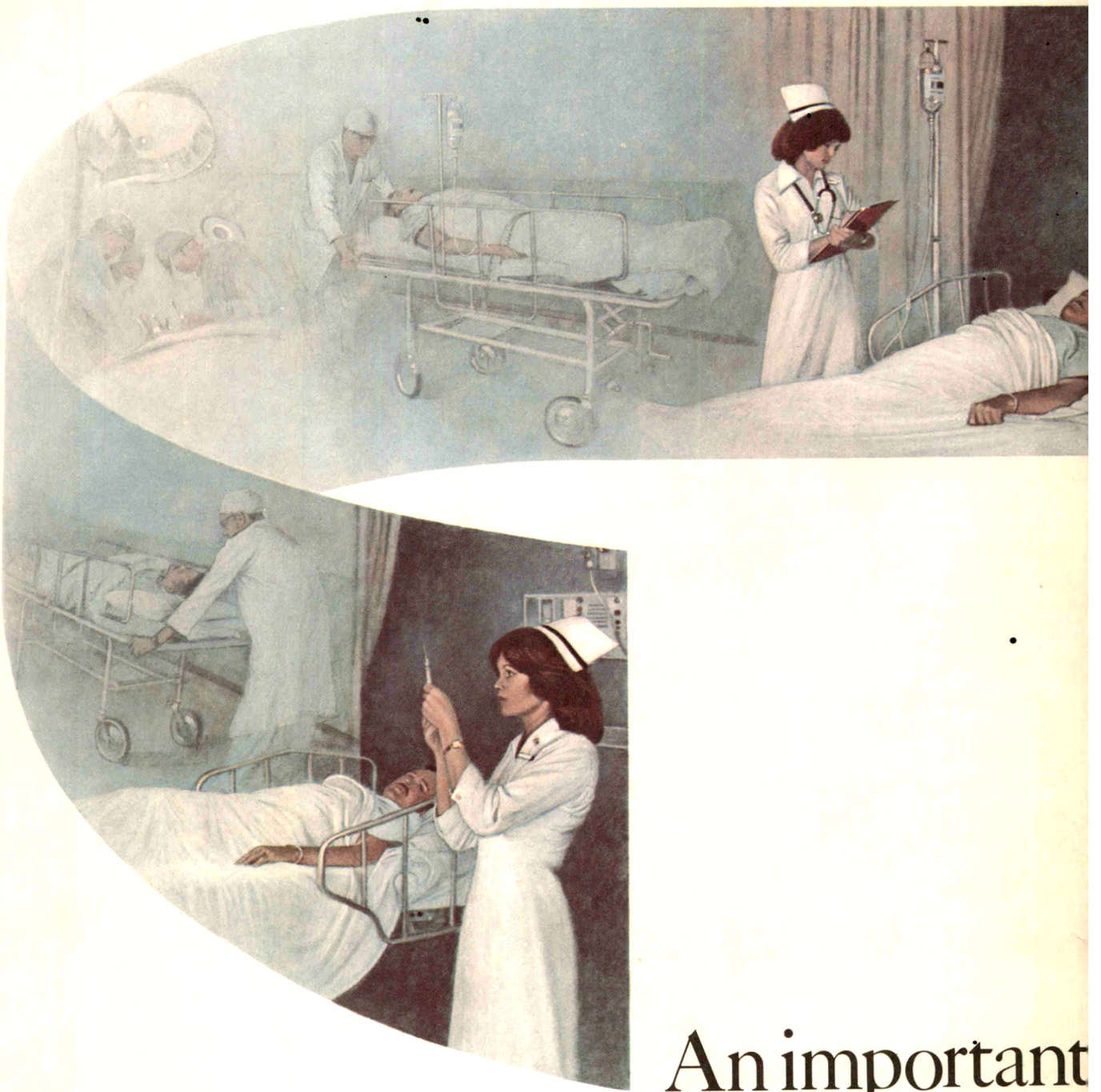
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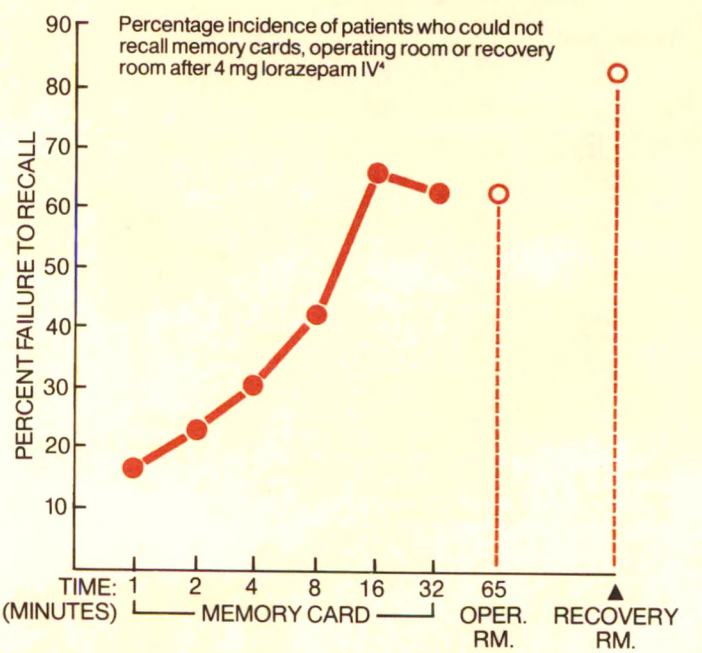
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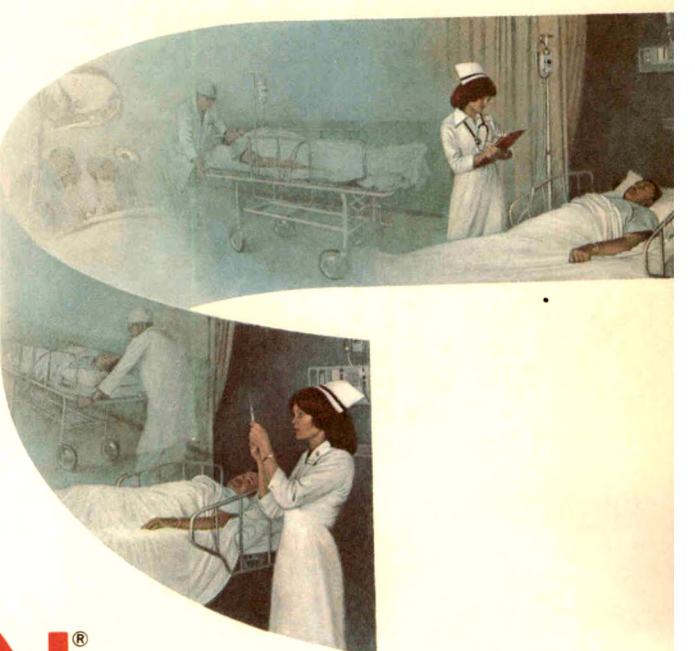
Ativan Injection can be used with atropine sulfate, narcotic analgesics, other parenterally used analgesics, commonly used anesthetics and muscle relaxants. Concomitant use with scopolamine is not advisable, since it may lead to increased sedation, hallucinations and irrational behavior.

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References:
1. Data on file, Wyeth Laboratories.
2. Simpson PJ, Eltringham RJ: to be published.
3. Conner JT, Parson N, Katz RL, et al: Clin Pharmacol Ther *19*:24-29, 1976.
4. Conner JT, Katz RL, Bellville JW, et al: J Clin Pharmacol *18*:285-292, 1978.
5. Heisterkamp DV, Cohen PJ: Br J Anaesth *47*:79-81, 1975.
6. Greenblatt DJ, Shader RI: N Engl J Med *299*:1342-1344, 1978.
7. Graham CW, Pagano RR, Conner JT: Anaesthesia *33*:188-191, 1978.

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Lorazepam is a nearly white powder almost insoluble in water. Each ml of sterile injection contains either 2.0 or 4.0 mg lorazepam, 0.18 ml polyethylene glycol 400 in propylene glycol with 2.0% benzyl alcohol as preservative.

CLINICAL PHARMACOLOGY: IV or IM administration of recommended dose of 2-4 mg lorazepam injection to adult patients is followed by dose related effects of sedation (sleepiness or drowsiness), relief of preoperative anxiety and lack of recall of events related to day of surgery in most patients. The clinical sedation (sleepiness or drowsiness) thus noted is such that most patients are able to respond to simple instructions whether they give appearance of being awake or asleep. Lack of recall is relative rather than absolute, as determined under conditions of careful patient questioning and testing, using props designed to enhance recall. Most patients under these reinforced conditions had difficulty recalling perioperative events, or recognizing props from before surgery. Lack of recall and recognition was optimum within 2 hours after IM and 15-20 minutes after IV injection.

Intended effects of recommended adult dose of lorazepam injection usually last 6-8 hours. In rare instances and where patients received greater than recommended dose, excessive sleepiness and prolonged lack of recall were noted. As with other benzodiazepines, unsteadiness, enhanced sensitivity to CNS depressant effects of ethyl alcohol and other drugs were noted in isolated and rare cases for greater than 24 hours.

Studies in healthy adult volunteers reveal that IV lorazepam in doses up to 3.5 mg/70 kg does not alter sensitivity to respiratory stimulating effect of carbon dioxide and does not enhance respiratory depressant effects of doses of meperidine up to 100 mg/70 kg (also determined by carbon dioxide challenge) as long as patients remain sufficiently awake to undergo testing. Upper airway obstruction was observed in rare instances where the patient received greater than recommended dose, and was excessively sleepy and difficult to arouse. (See WARNINGS and ADVERSE REACTIONS.)

Clinically employed doses of lorazepam injectable do not greatly affect the circulatory system in the supine position or employing a 70 degree tilt test. Doses of 8-10 mg of IV lorazepam (2 to 2.5 times maximum recommended dosage) will produce loss of lid reflexes within 15 minutes.

Studies in six (6) healthy young adults who received lorazepam injection and no other drugs revealed that visual tracking (the ability to keep a moving line centered) was impaired for a mean of eight (8) hours following 4 mg IM lorazepam and four (4) hours following 2 mg IM with considerable subject variation. Similar findings were noted with pentobarbital 150 and 75 mg. Although this study showed both lorazepam and pentobarbital interfered with eye-hand coordination, data are insufficient to predict when it would be safe to operate a motor vehicle or engage in hazardous occupation or sport.

INDICATIONS AND USAGE: In adults—for preanesthetic medication, producing sedation (sleepiness or drowsiness), relief of anxiety, and decreased ability to recall events related to day of surgery. Most useful in patients anxious about surgical procedure who prefer diminished recall of events of day of surgery.

CONTRAINDICATIONS: Known sensitivity to benzodiazepines or vehicle (polyethylene glycol, propylene glycol, and benzyl alcohol) or acute narrow angle glaucoma. Intra-arterial injection is contraindicated because, as with other injectable benzodiazepines, inadvertent intra-arterial injection may produce arteriospasm resulting in gangrene which may require amputation. (See Warnings)

WARNINGS: PRIOR TO IV USE, LORAZEPAM SHOULD BE DILUTED WITH EQUAL AMOUNT OF COMPATIBLE DILUENT (SEE DOSAGE AND ADMINISTRATION). IV INJECTION SHOULD BE MADE SLOWLY AND WITH REPEATED ASPIRATION. CAREFULLY DETERMINE THAT INJECTION WILL NOT BE INTRA-ARTERIAL AND PERIVASCULAR EXTRAVASATION WILL NOT OCCUR. PARTIAL AIRWAY OBSTRUCTION MAY OCCUR IN HEAVILY SEDATED PATIENTS. IV LORAZEPAM, GIVEN ALONE IN GREATER THAN RECOMMENDED DOSE, OR AT RECOMMENDED DOSE AND ACCOMPANIED BY OTHER DRUGS USED DURING ANESTHESIA, MAY PRODUCE HEAVY SEDATION; THEREFORE, EQUIPMENT TO MAINTAIN PATENT AIRWAY AND SUPPORT RESPIRATION AND VENTILATION SHOULD BE AVAILABLE.

No evidence now supports lorazepam injection in coma, shock or acute alcohol intoxication. Since the liver is the most likely site of conjugation and since excretion of conjugated lorazepam (glucuronide), is renal, lorazepam is not recommended in hepatic and/or renal *failure*. This does not preclude its use in patients with mild to moderate hepatic or renal disease. When injectable lorazepam is used in mild to moderate hepatic or renal disease, consider lowest effective dose since drug effect may be prolonged. Experience with other benzodiazepines and limited experience with parenteral lorazepam demonstrated that tolerance to concomitant alcohol and other CNS depressants is diminished. As with similar CNS-acting drugs, patients receiving injectable lorazepam should not operate machinery or motor vehicles or engage in hazardous occupations for 24 to 48 hours. Impairment of performance may persist for greater intervals because of extremes of age, other concomitant drugs, stress of surgery or general condition of patient. Clinical trials showed patients over 50 may have more profound and prolonged sedation with IV use. Ordinarily an initial dose of 2 mg may be adequate, unless greater degree of lack of recall is desired. As with all CNS depressants, exercise care in patients given injectable lorazepam since premature ambulation may result in injury from falling. There is no added beneficial effect from adding scopolamine to injectable lorazepam; their combined effect may result in increased incidence of sedation, hallucination and irrational behavior.

Pregnancy: LORAZEPAM GIVEN TO PREGNANT WOMEN MAY CAUSE FETAL DAMAGE. Increased risk of congenital malformations with use of minor tranquilizers (chlordiazepoxide, diazepam, meprobamate) during first trimester of pregnancy was suggested in several studies. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide. Lorazepam injection should not be used during pregnancy because of insufficient data on obstetrical safety, including its use in cesarean section. Reproductive studies performed in mice, rats, and two strains of rabbits showed occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in concurrent control group, they have been reported to occur randomly in historical controls. At doses of 40 mg/kg p.o. or 4 mg/kg IV and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses.

Endoscopic Procedures: There are insufficient data to support lorazepam injection for outpatient endoscopic procedures. Inpatient endoscopic procedures require adequate recovery room observations. Pharyngeal reflexes are not impaired when lorazepam injection is used for per-oral endoscopic procedures, therefore adequate topical or regional anesthesia is recommended to minimize reflex activity associated with such procedures.

PRECAUTIONS: General: Bear in mind additive CNS effects of other drugs, e.g. phenothiazines, narcotic analgesics, barbiturates, antidepressants, scopolamine and MAO inhibitors when these drugs are used concomitantly with or during period of recovery from lorazepam injection. (See CLINICAL PHARMACOLOGY and WARNINGS.) Use extreme care in giving lorazepam injection to elderly or very ill patients, or those with limited pulmonary reserve, because of possible underventilation and/or hypoxic cardiac arrest. Resuscitative equipment for ventilatory support should be readily available. (See WARNINGS and DOSAGE and ADMINISTRATION.) When lorazepam is used IV as premedicant prior to regional or local anesthesia, excessive sleepiness or drowsiness may possibly interfere with patient cooperation to determine anesthesia levels. This is most likely when more than 0.05 mg/kg is given and narcotic analgesics are used concomitantly with the recommended dose. (See ADVERSE REACTIONS.)

Information for Patients: As appropriate, inform patients of pharmacological effects, e.g. sedation, relief of anxiety and lack of recall, and duration of these effects (about 8 hours), so they may adequately perceive risks as well as benefits from its use. Caution patients who receive lorazepam injection as premedicant that driving automobiles or operating hazardous machinery, or engaging in hazardous sports should be delayed for 24 to 48 hours after injection. Sedatives, tranquilizers, and narcotic analgesics given with injectable lorazepam may produce more prolonged and profound effect, taking the form of excessive sleepiness or drowsiness, and rarely interfering with recall and recognition of events of day of surgery and the day after. Getting out of bed unassisted may result in falling and injury if undertaken within 8 hours of receiving lorazepam injection. Alcoholic beverages should not be used for at least 24 to 48 hours after lorazepam injection due to additive effects on CNS depression seen with benzodiazepines in general. Elderly patients should be told lorazepam injection may make them very sleepy for longer than 6 to 8 hours after surgery.

Laboratory Tests: In clinical trials no laboratory test abnormalities were identified with single or multiple doses of lorazepam injection. Tests included: CBC, urinalysis, SGOT, SGPT, bilirubin, alkaline phosphatase, LDH, cholesterol, uric acid, BUN, glucose, calcium, phosphorus and total proteins.

Drug Interactions: Lorazepam injection, like other injectable benzodiazepines, produces CNS depression when given with ethyl alcohol, phenothiazines, barbiturates, MAO inhibitors and other antidepressants. When scopolamine is used concomitantly with injectable lorazepam increased incidence of sedation, hallucinations and irrational behavior was observed.

Drug/Laboratory Test Interactions: No laboratory test abnormalities were identified when lorazepam was given alone or concomitantly with another drug, e.g. narcotic analgesics, inhalation anesthetics, scopolamine, atropine, and various tranquilizing agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No evidence of carcinogenic potential emerged in rats and mice during an 18-month study with oral lorazepam. No studies regarding mutagenesis have been performed. Pre-implantation study in rats, performed with oral lorazepam at a 20 mg/kg dose, showed no impairment of fertility.

Pregnancy: Pregnancy Category D. See WARNINGS section.

Labor and Delivery: There are insufficient data for lorazepam injection in labor and delivery, including cesarean section; therefore, this use is not recommended.

Nursing Mothers: Do not give injectable lorazepam to nursing mothers, because like other benzodiazepines, lorazepam may possibly be excreted in human milk and sedate the infant.

Pediatric Use: There are insufficient data to support efficacy or make dosage recommendations for injectable lorazepam in patients under 18 years; therefore, such use is not recommended.

ADVERSE REACTIONS: CNS: Most frequent adverse effects with injectable lorazepam are extensions of drug's CNS depressant effects. Incidence varied from one study to another, depending on dosage, route, use of other CNS depressants, and investigator's opinion concerning degree and duration of desired sedation. Excessive sleepiness and drowsiness were main side effects. This interfered with patient cooperation in about 6% (25/446) of patients undergoing regional anesthesia in that they were unable to assess levels of anesthesia in regional blocks or with caudal anesthesia. Patients over 50 years had higher incidence of excessive sleepiness or drowsiness compared with those under 50 (21/106 vs 24/245) when lorazepam was given IV (see DOSAGE and ADMINISTRATION). On rare occasion (3/1580) patient was unable to give personal identification on arrival in operating room, and one patient fell when attempting premature ambulation in postoperative period. Symptoms such as restlessness, confusion, depression, crying, sobbing, and delirium occurred in about 1.3% (20/1580). One patient injured himself postoperatively by picking at his incision. Hallucinations were present in about 1% (14/1580) of patients, and were visual and self-limiting. An occasional patient complained of dizziness, diplopia and/or blurred vision. Depressed hearing was infrequently reported during peak effect period. An occasional patient had prolonged recovery room stay, because of excessive sleepiness or some form of inappropriate behavior (latter seen most commonly when scopolamine given concomitantly as premedicant). Limited information from patients discharged day after receiving injectable lorazepam showed one patient complained of some unsteadiness of gait and reduced ability to perform complex mental functions. Enhanced sensitivity to alcoholic beverages was reported more than 24 hours after injectable lorazepam, similar to experience with other benzodiazepines.

Local Effects: IM lorazepam resulted in pain at injection site, a sensation of burning, or observed redness in the same area in a very variable incidence from one study to another. Overall incidence of pain and burning was about 17% (146/859) in immediate postinjection period, and about 1.4% (12/859) at 24-hour observation time. Reactions at injection site (redness) occurred in about 2% (17/859) in immediate postinjection period, and were present 24 hours later in about 0.8% (7/859). IV lorazepam resulted in pain in 13/771 patients or about 1.6% immediately post-injection and 24 hours later 4/771 patients or about 0.5% still complained of pain. Redness did not occur immediately post IV but was noted in 19/771 patients at 24-hour period (incidence is similar to that observed with IV infusion before lorazepam was given).

Cardiovascular System: Hypertension (0.1%) and hypotension (0.1%) were occasionally observed after patients received injectable lorazepam.

Respiratory System: Five patients (5/446) who underwent regional anesthesia were observed to have partial airway obstruction. This was believed due to excessive sleepiness at time of procedure, and resulted in temporary underventilation. Immediate attention to the airway, employing usual countermeasures, will usually suffice to manage this (see also CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS).

Other Adverse Experiences: Skin rash, nausea and vomiting were occasionally noted in patients who received injectable lorazepam with other drugs during anesthesia and surgery.

DRUG ABUSE AND DEPENDENCE: As with other benzodiazepines, lorazepam injection has a low potential for abuse and may lead to limited dependence. Although there are no such clinical data for injectable lorazepam, repeated doses over prolonged period of time may result in limited physical and psychological dependence.

OVERDOSAGE: Overdosage of benzodiazepines is usually manifested by varying degrees of CNS depression ranging from drowsiness to coma. In mild cases symptoms include drowsiness, mental confusion and lethargy; in more serious cases ataxia, hypotonia, hypotension, hypnosis, stages one to three coma, and very rarely death. Treatment of overdosage is mainly supportive until drug is eliminated. Carefully monitor vital signs and fluid balance. Maintain adequate airway and assist respiration as needed. With normally functioning kidneys, forced diuresis with intravenous fluids and electrolytes may accelerate elimination of benzodiazepines. In addition, osmotic diuretics such as mannitol may be effective as adjunctive measures. In more critical situations, renal dialysis and exchange blood transfusions may be indicated. Published reports indicate that IV infusion of 0.5 to 4 mg physostigmine at rate of 1 mg/minute may reverse symptoms and signs suggestive of central anticholinergic overdose (confusion, memory disturbance, visual disturbances, hallucinations, delirium); however, hazards associated with physostigmine (i.e., induction of seizures) should be weighed against possible clinical benefit.

DOSAGE AND ADMINISTRATION: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not use if solution is discolored or contains a precipitate.

Intramuscular Injection: For designated indications as premedicant, usual IM dose of lorazepam is 0.05 mg/kg up to maximum of 4 mg. As with all premedicants, individualize dose. (See also CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.) Doses of other CNS depressants should ordinarily be reduced. (See PRECAUTIONS.) *For optimum effect, measured as lack of recall, administer lorazepam IM at least 2 hours before anticipated operative procedure.* Administer narcotic analgesics at usual preoperative time. There are insufficient efficacy data to make dosage recommendations for IM lorazepam in patients under 18 years; therefore, such use is not recommended.

Intravenous Injection: For the primary purpose of sedation and relief of anxiety, usual recommended initial IV dose of lorazepam is 2 mg total, or 0.02 mg/lb (0.044 mg/kg), whichever is smaller. This dose will suffice for sedating most adults, and should not ordinarily be exceeded in patients over 50 years. In patients in whom greater likelihood of lack of recall for perioperative events would be beneficial, larger doses—as high as 0.05 mg/kg up to total of 4 mg—may be given. (See CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.) Doses of other injectable CNS depressants should ordinarily be reduced. (See PRECAUTIONS.) *For optimum effect, measured as lack of recall, IV lorazepam should be administered 15-20 minutes before anticipated operative procedure.* EQUIPMENT NECESSARY TO MAINTAIN A PATENT AIRWAY SHOULD BE IMMEDIATELY AVAILABLE PRIOR TO IV USE OF LORAZEPAM (see WARNINGS). There are insufficient efficacy data to make dosage recommendations for IV lorazepam in patients under 18 years; therefore, such use is not recommended.

Administration: When given IM, lorazepam injection, undiluted, should be injected deep in muscle mass. Injectable lorazepam can be used with atropine sulfate, narcotic analgesics, other parenterally used analgesics, commonly used anesthetics, and muscle relaxants. Immediately prior to IV use, lorazepam injection must be diluted with an equal volume of compatible solution. When properly diluted the drug may be injected directly into a vein or into the tubing of an existing IV infusion. Rate of injection should not exceed 2.0 mg per minute. Lorazepam injection is compatible for dilution purposes with: Sterile Water for Injection, USP, Sodium Chloride Injection, USP, 5% Dextrose Injection, USP.

HOW SUPPLIED: Ativan® (lorazepam) injection, Wyeth, is available in multiple-dose vials and in TUBEX® Sterile Cartridge-Needle Units.

2 mg/ml, NDC 0008-0581; 10 ml vial and 1 ml fill in 2 ml TUBEX.
4 mg/ml, NDC 0008-0570; 10 ml vial and 1 ml fill in 2 ml TUBEX.

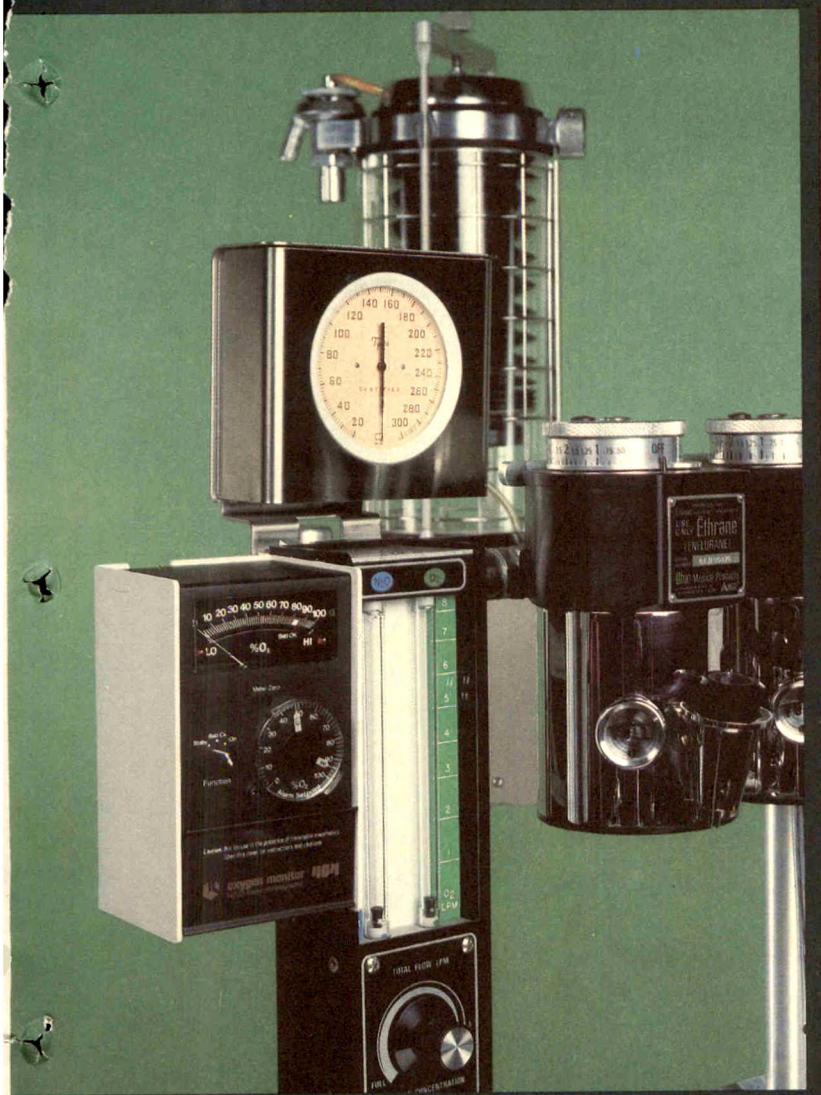
For IM or IV injection.

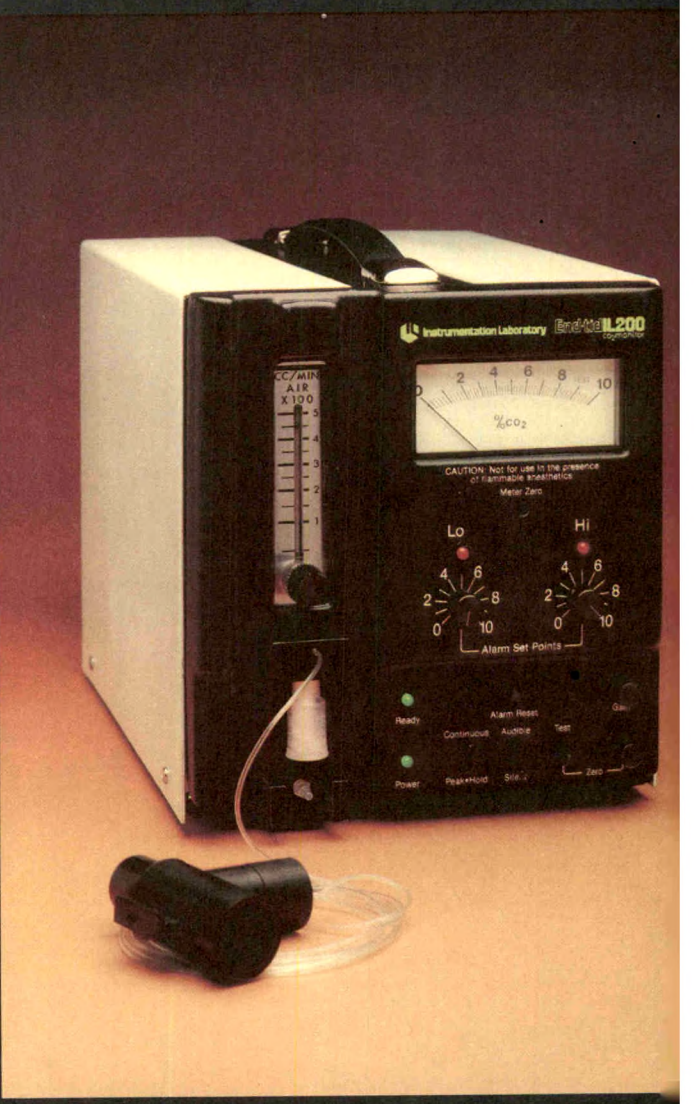
Protect from light. Keep in refrigerator.

Directions for Dilution for IV Use: To dilute, adhere to following procedure: For TUBEX—(1) Extrude entire amount of air in half-filled TUBEX. (2) Slowly aspirate desired volume of diluent. (3) Pull back slightly on plunger to provide additional mixing space. (4) Immediately mix contents thoroughly by gently inverting TUBEX repeatedly until homogenous solution results. Do not shake vigorously, as this will result in air entrapment. For Vial—Aspirate desired amount of lorazepam injection into syringe. Then proceed as described under TUBEX.

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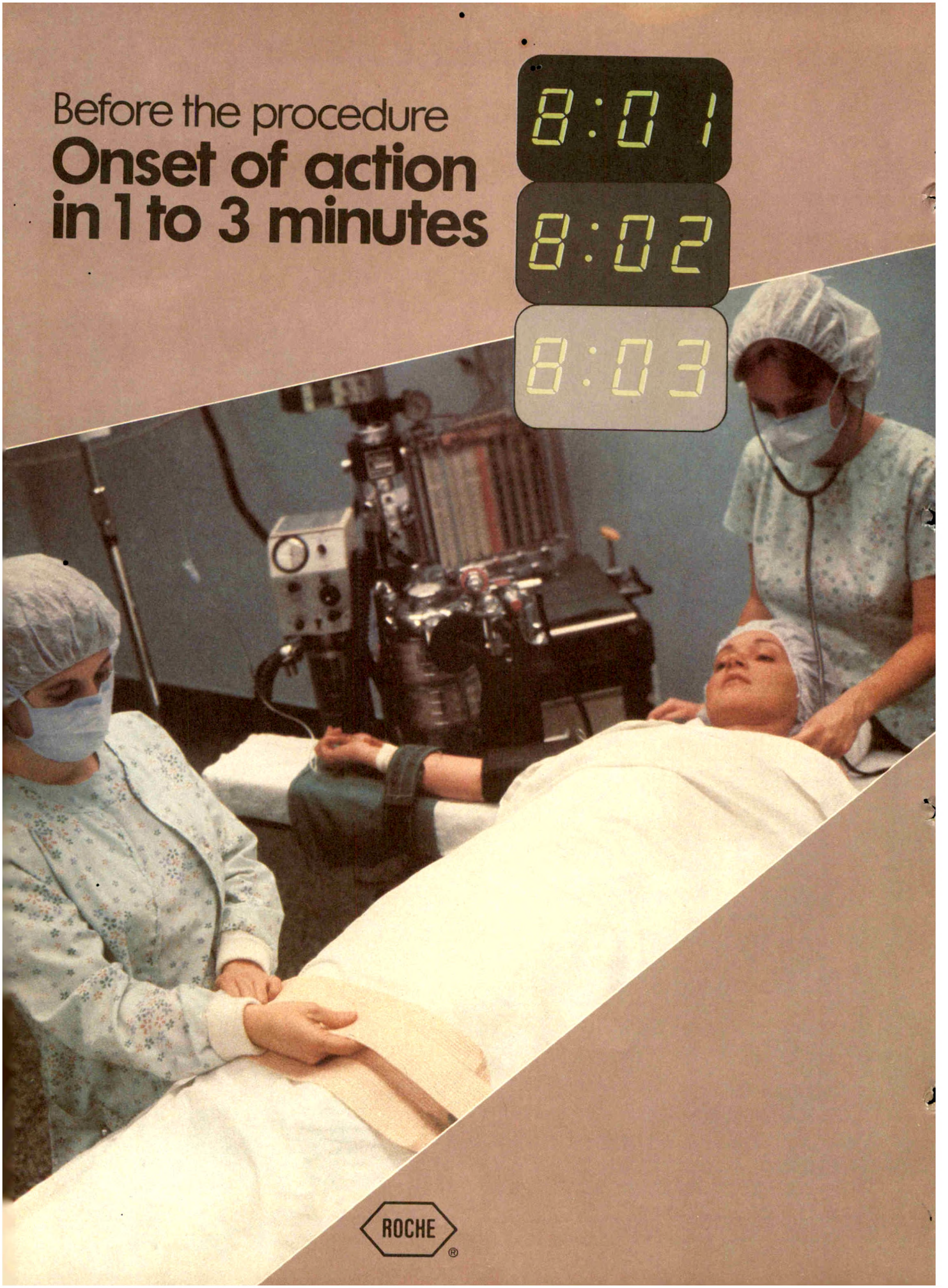
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- Calm relaxed patient, better prepared for the procedure.
- A proven record of safety and performance.
- Does not normally compromise cardiac or respiratory function. Resuscitative equipment should be readily available.
- Use with care in elderly, very ill and patients with limited pulmonary reserve (see Warnings section on following page).
- Narcotic dosage can and should be reduced.

Injectable **Valium® I.V.**
diazepam/Roche (IV)

A pattern of action that meets your needs

Please see summary of product information on next page.

Improved Tel-E-Ject®

10-mg Disposable Syringe (5 mg/ml)

scale on both sides of barrel eases visibility during administration





Injectable Valium® I.V.

diazepam/Roche

10-ml vials
2-ml ampuls } 5 mg/ml

Please consult complete product information, a summary of which follows:

Contraindications: Hypersensitivity; acute narrow angle glaucoma; may be used in patients with open angle glaucoma receiving appropriate therapy.

Warnings: *To reduce the possibility of venous thrombosis, phlebitis, local irritation, swelling, and, rarely, vascular impairment when used I.V.: inject slowly, taking at least one minute for each 5 mg (1 ml) given; do not use small veins, i.e., dorsum of hand or wrist; use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute Valium (diazepam/Roche) with other solutions or drugs in syringe or infusion flask. If it is not feasible to administer Valium directly I.V., it may be injected slowly through the infusion tubing as close as possible to the vein insertion.*

Administer with extreme care to elderly, very ill, those with limited pulmonary reserve because of possibility of apnea and/or cardiac arrest; concomitant use of barbiturates, alcohol or other CNS depressants increases depression with increased risk of apnea; have resuscitative facilities available. When used with narcotic analgesic, eliminate or reduce narcotic dosage at least ⅓, administer in small increments. Should not be administered to patients in shock, coma, acute alcoholic intoxication with depression of vital signs. As with most CNS-acting drugs, caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).

Has precipitated tonic status epilepticus in patients treated for petit mal status or petit mal variant status.

Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation after long use of excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after long, continuous use at high therapeutic levels. After extended therapy, gradually taper dosage.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations, as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Not recommended for OB use.

Efficacy/safety not established in neonates (age 30 days or less); prolonged CNS depression observed. In children, give slowly (up to 0.25 mg/kg over 3 minutes) to avoid apnea or prolonged somnolence; can be repeated after 15 to 30 minutes. If no relief after third administration, appropriate adjunctive therapy is recommended.

Precautions: Although promptly controlled, seizures may return; re-administer if necessary; not recommended for long-term maintenance therapy.

If combined with other psychotropics or anticonvulsants, carefully consider individual pharmacologic effects—particularly with known compounds which may potentiate action of Valium (diazepam/Roche), *i.e.*, phenothiazines, narcotics, barbiturates, MAO inhibitors, antidepressants. Protective measures indicated in highly anxious patients with accompanying depression who may have suicidal tendencies. Observe usual precautions in impaired hepatic function; avoid accumulation in patients with compromised kidney function. Laryngospasm/increased cough reflex are possible during peroral endoscopic procedures; use topical anesthetic, have necessary countermeasures available. Hypotension or muscular weakness possible, particularly when used with narcotics, barbiturates or alcohol. Use lower doses (2 to 5 mg) for elderly/debilitated.

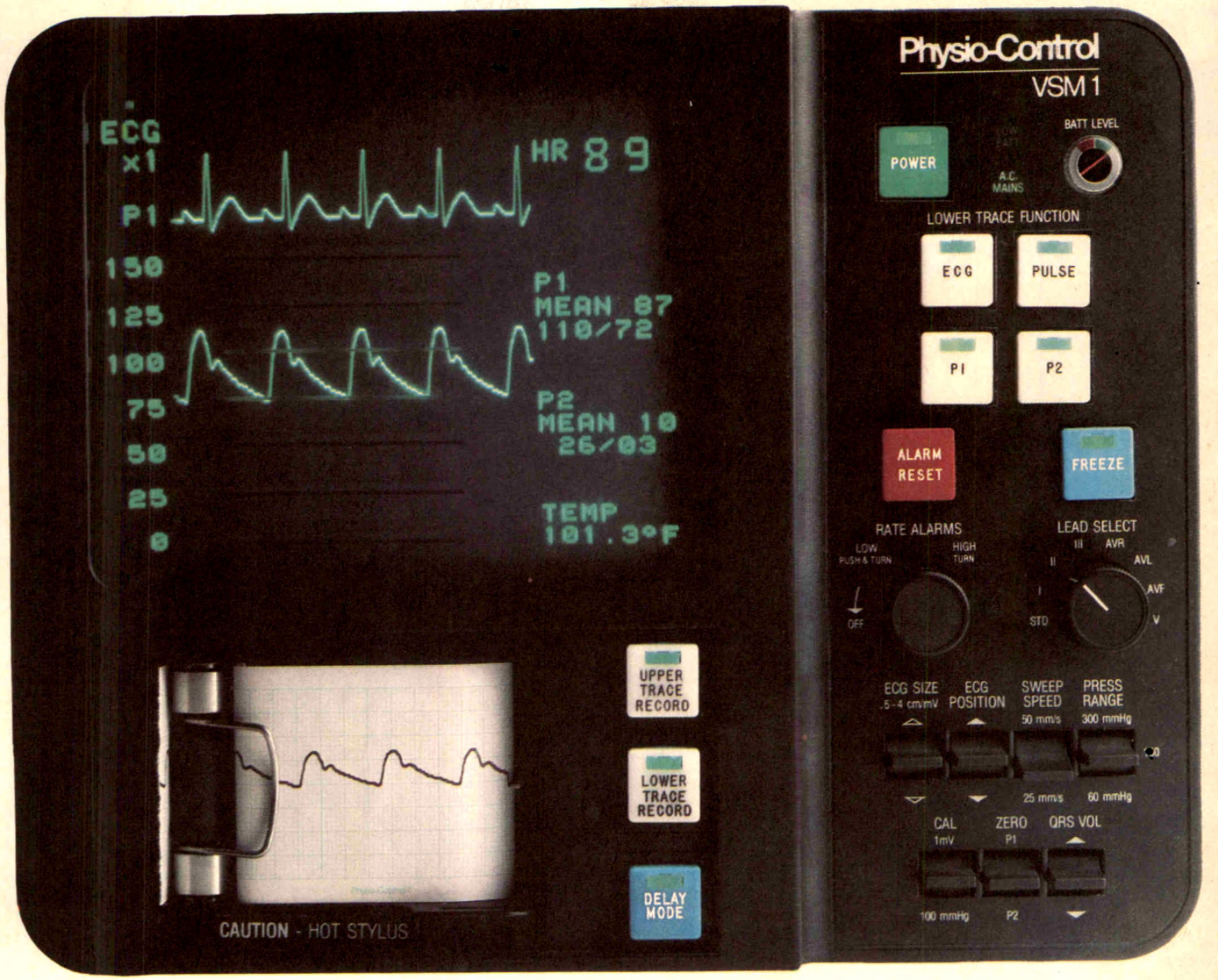
Adverse Reactions: Drowsiness, fatigue, ataxia, venous thrombosis/phlebitis at injection site, confusion, depression, dysarthria, headache, hypoactivity, slurred speech, syncope, tremor, vertigo, constipation, nausea, incontinence, changes in libido, urinary retention, bradycardia, cardiovascular collapse, hypotension, blurred vision, diplopia, nystagmus, urticaria, skin rash, hiccups, changes in salivation, neutropenia, jaundice. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Cough, depressed respiration, dyspnea, hyperventilation, laryngospasm/pain in throat and chest have been reported in peroral endoscopic procedures. Isolated reports of neutropenia, jaundice; periodic blood counts, liver function tests advisable during long-term therapy. Minor EEG changes, usually low-voltage fast activity, of no known significance.

Management of Overdosage: Manifestations include somnolence, confusion, coma, diminished reflexes. Monitor respiration, pulse, blood pressure; employ general supportive measures, I.V. fluids, adequate airway. Hypotension may be combated by the use of levarterenol or metaraminol. Dialysis is of limited value.

Supplied: Ampuls, 2 ml, boxes of 10; Vials, 10 ml, boxes of 1; Tel-E-Ject® (disposable syringes), 2 ml, boxes of 10. Each ml contains 5 mg diazepam compounded with 40% propylene glycol, 10% ethyl alcohol, 5% sodium benzoate and benzoic acid as buffers, and 1.5% benzyl alcohol as preservative.

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We should also like to emphasize that the VSM-1 has been designed and engineered to the highest possible standards of reliability. It has been subjected to extensive clinical testing and analysis, including accelerated life tests and reliability demonstration testing. All critical components are preconditioned and rigorously tested.

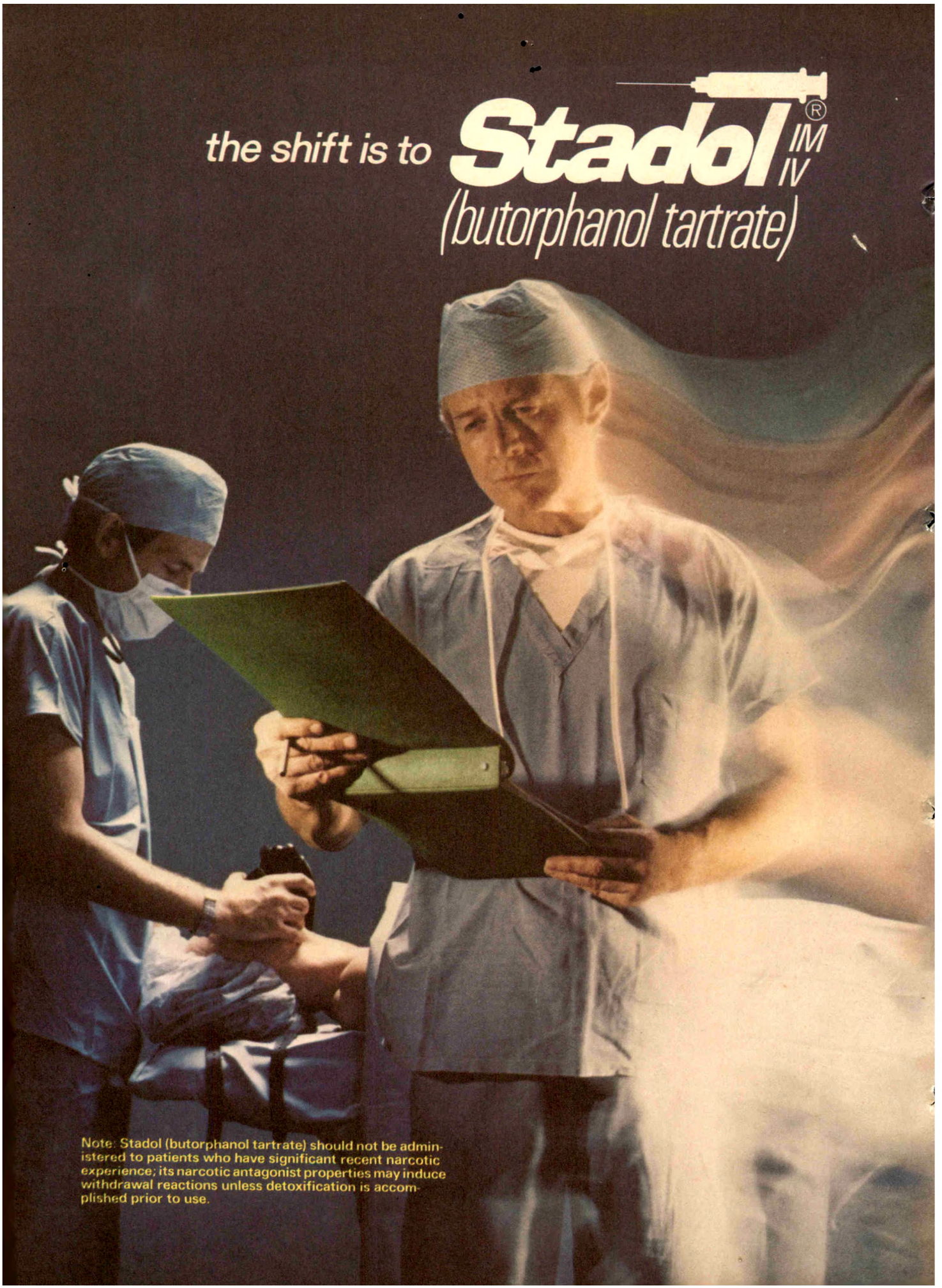
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IM
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(butorphanol tartrate)
Note: Stadol (butorphanol tartrate) should not be administered to patients who have significant recent narcotic experience; its narcotic antagonist properties may induce withdrawal reactions unless detoxification is accomplished prior to use.


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preoperatively
intraoperatively
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■ proven analgesic efficacy—as a pre- and postoperative agent...for patients in labor... as the analgesic component of balanced anesthesia
■ fast acting—onset of action within 10 minutes IM, very rapidly IV; peak analgesic activity within 30-60 minutes IM, more rapidly IV
■ limited respiratory depressant potential—2 mg of Stadol produces a degree of respiratory depression similar to that of 10 mg of morphine or 70 mg of meperidine—unlike these agents, doubling the Stadol dose to 4 mg does not appreciably increase the magnitude of respiratory depression
■ favorable side effect profile—low physical dependence liability, little nausea or vomiting, infrequent constipation
■ few CNS effects other than sedation—the reported incidence of euphoria and hallucinations is less than 1%
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proven performance in the relief of moderate to severe pain
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STADOL® (butorphanol tartrate)
For complete information, consult Official Package Circular.

(2) 12/10/79

INDICATIONS AND USAGE—Stadol is recommended for the relief of moderate to severe pain. Stadol can also be used for preoperative or preanesthetic medication, as a supplement to balanced anesthesia, and for the relief of prepartum pain.

CONTRAINDICATIONS—Stadol should not be administered to patients who have been shown to be hypersensitive to it.

WARNINGS—Patients Physically Dependent on Narcotics: Because of its antagonist properties, Stadol is not recommended for patients physically dependent on narcotics. Detoxification in such patients is required prior to use.
Due to the difficulty in assessing addiction in patients who have recently received substantial amounts of narcotic medication, caution should be used in the administration of Stadol. Detoxification of such patients prior to usage should be carefully considered.

Drug Dependence: Special care should be exercised in administering Stadol to emotionally unstable patients and to those with a history of drug misuse. When long-term therapy is contemplated, such patients should be closely supervised. Even though Stadol has a low physical dependence liability, care should be taken that individuals who may be prone to drug abuse are closely supervised. It is important to avoid increases in dose and frequency of injections by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

Head Injury and Increased Intracranial Pressure: Although there is no clinical experience in patients with head injury, it can be assumed that Stadol, like other potent analgesics, elevates cerebrospinal fluid pressure. Therefore the use of Stadol in cases of head injury can produce effects (e.g., miosis) which may obscure the clinical course of patients with head injuries. In such patients Stadol must be used with extreme caution and only if its use is deemed essential.

Cardiovascular Effects: Because Stadol increases the work of the heart, especially the pulmonary circuit, the use of this drug in acute myocardial infarction or in cardiac patients with ventricular dysfunction or coronary insufficiency should be limited to those who are hypersensitive to morphine sulfate or meperidine.

PRECAUTIONS—Certain Respiratory Conditions: Because Stadol causes some respiratory depression, it should be administered only with caution and low dosage to patients with respiratory depression (e.g., from other medication, uremia, or severe infection), severely limited respiratory reserve, bronchial asthma, obstructive respiratory conditions, or cyanosis.

Impaired Renal or Hepatic Function: Although laboratory tests have not indicated that Stadol causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Extensive liver disease may predispose to greater side effects and greater activity from the usual clinical dose, possibly the result of decreased metabolism of the drug by the liver.

Biliary Surgery: Clinical studies have not been done to establish the safety of Stadol administration to patients about to undergo surgery of the biliary tract.

Usage as a Preoperative or Preanesthetic Medication: Slight increases in systolic blood pressure may occur, therefore caution should be employed when Stadol is used in the hypertensive patient.

Usage in Balanced Anesthesia: The use of pancuronium in combination with Stadol may cause an increase in conjunctival changes.

Usage in Pregnancy: The safety of Stadol for use in pregnancy prior to the labor period has not been established; therefore, this drug should be used in pregnant patients only when in the judgment of the physician its use is deemed essential to the welfare of the patient.
Reproduction studies have been performed in rats, mice and rabbits and have revealed no evidence of impaired fertility or harm to the fetus due to Stadol at about 2.5 to 5 times the human dose.

Usage in Labor and Delivery: Safety to the mother and fetus following administration of Stadol during labor has been established. Patients receiving Stadol during labor have experienced no adverse effects other than those observed with commonly used analgesics. Stadol should be used with caution in women delivering premature infants.

Usage in Nursing Mothers: The use of Stadol in lactating mothers who are nursing their infants is not recommended since it is not known whether this drug is excreted in human milk. Stadol has been used safely for labor pain in mothers who subsequently nursed their infants.

Usage in Children: Safety and efficacy in children below age 18 years have not been established.

ADVERSE REACTIONS—The most frequent adverse reactions in 1250 patients treated with Stadol are: sedation (503, 40%), nausea (82, 6%), clammy/sweating (76, 6%).
Less frequent reactions are: headache (35, 3%), vertigo (33, 3%), floating feeling (33, 3%), dizziness (23, 2%), lethargy (19, 2%), confusion (15, 1%), lightheadedness (12, 1%).
Other adverse reactions which may occur (reported incidence of less than 1%) are:
CNS: nervousness, unusual dreams, agitation, euphoria, hallucinations
Autonomic: flushing and warmth, dry mouth, sensitivity to cold
Cardiovascular: palpitation, increase or decrease of blood pressure
Gastrointestinal: vomiting
Respiratory: slowing of respiration, shallow breathing
Dermatological: rash or hives
Eye: diplopia or blurred vision

OVERDOSAGE—Manifestations: Although there have been no experiences of overdosage with Stadol during clinical trials, this may occur due to accidental or intentional misuse as well as therapeutic use. Based on the pharmacology of Stadol, overdosage could produce some degree of respiratory depression and variable cardiovascular and central nervous system effects.

Treatment: The immediate treatment of suspected Stadol overdosage is intravenous naloxone. The respiratory and cardiac status of the patient should be evaluated constantly and appropriate supportive measures instituted, such as oxygen, intravenous fluids, vasopressors and assisted or controlled respiration.

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9th Edition, 1980

by

ARTHUR B. TARROW, M.D. and JAMES C. ERICKSON, III, M.D.,

PROFESSORS, JEFFERSON MEDICAL COLLEGE
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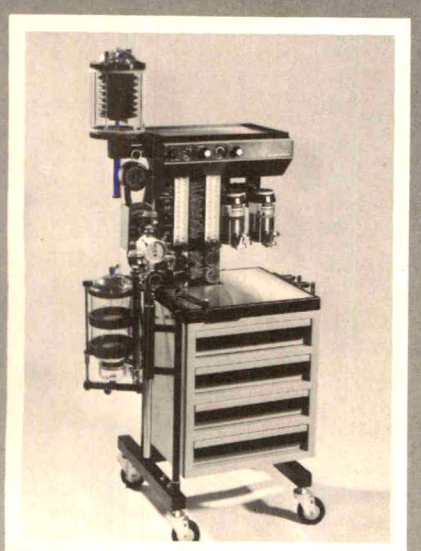
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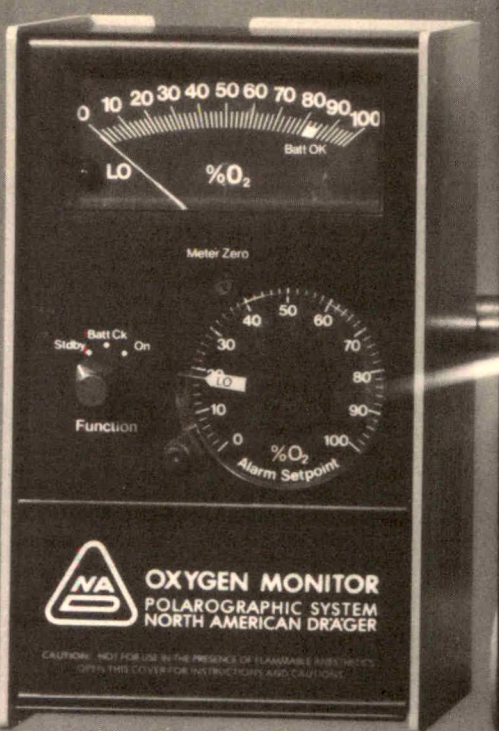
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Brief Summary (Please consult full package insert, enclosed in every package, before using Pavulon).

ACTIONS: Pavulon is a non-depolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform) on the myoneural junction.

Pavulon (pancuronium bromide) is antagonized by acetylcholine, anticholinesterases, and potassium ion. Its action is increased by inhalational anesthetics such as halothane, diethyl ether, enflurane and methoxyflurane, as well as quinine, magnesium salts, hypokalemia, some carcinomas, and certain antibiotics such as neomycin, streptomycin, clindamycin, kanamycin, gentamicin and bacitracin. The action of Pavulon may be altered by dehydration, electrolyte imbalance, acid-base imbalance, renal disease, and concomitant administration of other neuromuscular agents.

CONTRAINDICATIONS: Pavulon is contraindicated in patients known to be hypersensitive to the drug or to the bromide ion.

WARNINGS: PAVULON SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS, WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION.

In patients who are known to have myasthenia gravis small doses of Pavulon may have profound effects. A peripheral nerve stimulator is especially valuable in assessing the effects of Pavulon in such patients.

USAGE IN PREGNANCY: The safe use of pancuronium bromide has not been established with respect to the possible adverse effects upon fetal development. Therefore, it should not be used in women of childbearing potential and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the unknown hazards.

Pavulon may be used in operative obstetrics (Cesarean section), but reversal of pancuronium may be unsatisfactory in patients receiving magnesium sulfate for toxemia of pregnancy, because magnesium salts enhance neuromuscular blockade. Dosage should usually be reduced, as indicated, in such cases.

PRECAUTIONS: Although Pavulon has been used successfully in many patients with pre-existing pulmonary, hepatic, or renal disease, caution should be exercised in these situations. This is particularly true of renal disease since a major portion of administered Pavulon is excreted unchanged in the urine.

ADVERSE REACTIONS: Neuromuscular: the most frequently noted adverse reactions consist primarily of an extension of the drug's pharmacological actions beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle relaxation resulting in respiratory insufficiency or apnea. Inadequate reversal of the neuromuscular blockade by anticholinesterase agents has also been observed with Pavulon (pancuronium bromide) as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate.

Cardiovascular: A slight increase in pulse rate is frequently noted.

Gastrointestinal: Salivation is sometimes noted during very light anesthesia, especially if no anticholinergic premedication is used.

Skin: An occasional transient rash is noted accompanying the use of Pavulon.

Respiratory: One case of wheezing, responding to deepening of the inhalational anesthetic, has been reported.

DRUG INTERACTION: The intensity of blockade and duration of action of Pavulon is increased in patients receiving potent volatile inhalational anesthetics such as halothane, diethyl ether, enflurane and methoxyflurane.

Prior administration of succinylcholine, such as that used for endotracheal intubation, enhances the relaxant effect of Pavulon and the duration of action. If succinylcholine is used before Pavulon, the administration of Pavulon should be delayed until the succinylcholine shows signs of wearing off.

DOSAGE AND ADMINISTRATION: Pavulon should be administered only by or under the supervision of experienced clinicians. DOSAGE MUST BE INDIVIDUALIZED IN EACH CASE. See package insert for suggested dosages.

CAUTION: Federal law prohibits dispensing without prescription.

Reference:

1. Stanley and Liu, Anesth Analg 56:669, 1977

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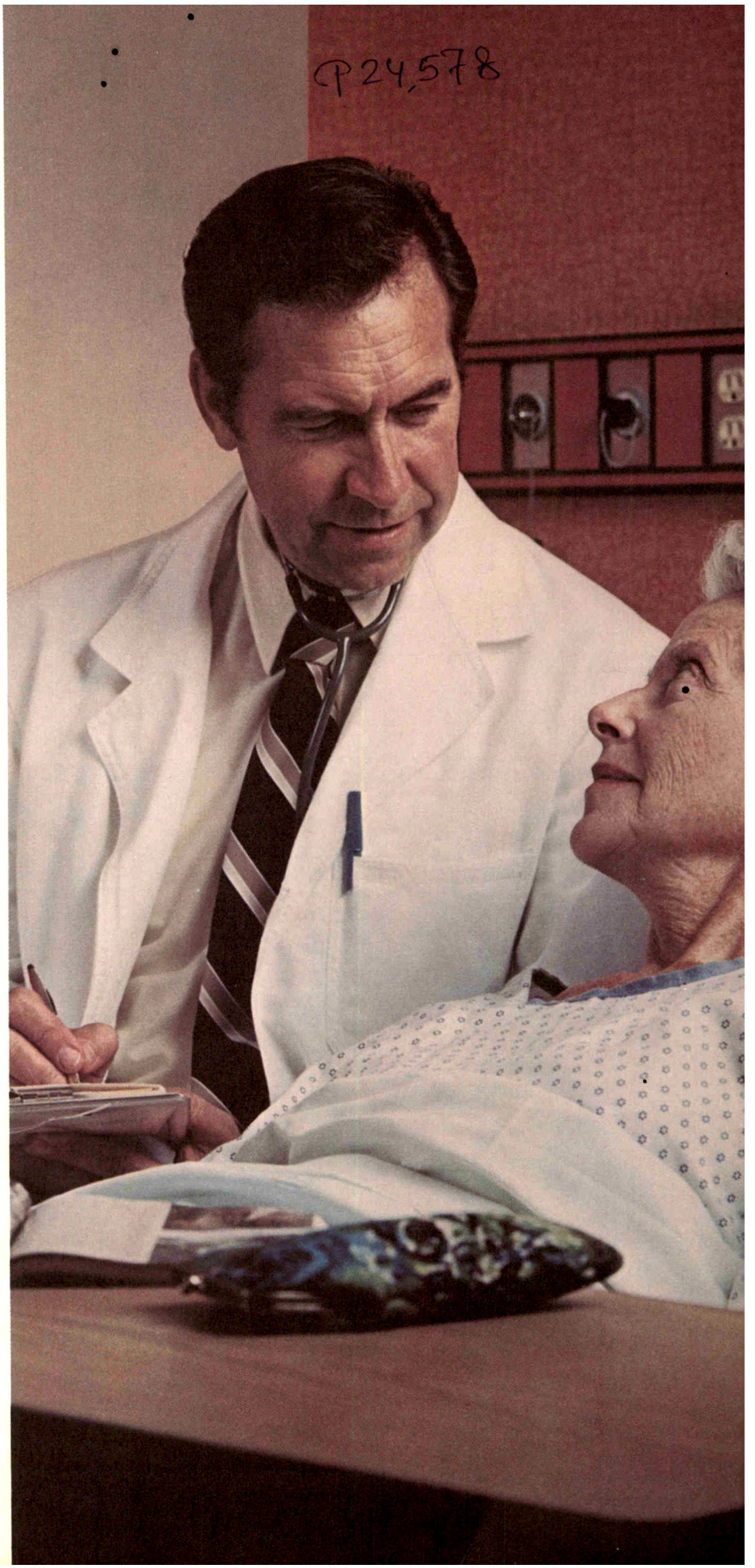
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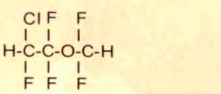
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DESCRIPTION

ETHRANE (enflurane) is a nonflammable inhalation anesthetic agent. It is 2-chloro-1, 1,2-trifluoroethyl difluoromethyl ether, molecular weight 184.5, and its structural formula is:



The boiling point is 56.5°C at 760 mm Hg, and the vapor pressure (mm Hg) is 175 at 20°C, 218 at 25°C, and 345 at 36°C. Vapor pressures can be calculated using the equation:

$\log_{10}P = A + B/T \quad A = 7.967$
$B = -1678.4$
$T = °C + 273.16$ (Kelvin)

The specific gravity (25°/25°C) is 1.517. The refractive index at 20° is 1.3026-1.3030. The blood/gas coefficient is 1.91 at 37°C and the oil/gas coefficient is 98.5 at 37°C. The M.A.C. (minimum alveolar concentration) in man is 1.68 percent in pure oxygen, 0.57 in 70% nitrous oxide and oxygen, and 1.17 in 30% nitrous oxide and oxygen.

ETHRANE is a clear, colorless, stable liquid whose purity exceeds 99.9 percent (area % by gas chromatography). No chemical stabilizers are added as these have been found, through controlled laboratory tests, to be unnecessary to maintain stability even in the presence of ultraviolet light. ETHRANE is stable to strong base and does not decompose in contact with soda lime and does not attack aluminum, tin, brass, iron or copper. The partition coefficients of ETHRANE at 25°C are 74 in conductive rubber and 120 in polyvinyl chloride.

CLINICAL PHARMACOLOGY

ETHRANE (enflurane) is an inhalation anesthetic. Induction and recovery from anesthesia with ETHRANE are rapid. ETHRANE has a mild, sweet odor. There is mild stimulus to salivation or tracheobronchial secretions when ETHRANE is used alone. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia changes rapidly with ETHRANE. ETHRANE reduces ventilation as depth of anesthesia increases. High pCO_2 levels can be obtained at deeper levels of anesthesia if ventilation is not supported. ETHRANE provokes a sigh response reminiscent of that seen with diethyl ether.

There is a decrease in blood pressure with induction of anesthesia, followed by a return to near normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding increases in hypotension. Heart rate remains relatively constant without significant bradycardia. Electrocardiographic monitoring or recordings indicate that cardiac rhythm remains stable. Elevation of the carbon dioxide level in arterial blood does not alter cardiac rhythm.

Studies in man indicate a considerable margin of safety in the administration of epinephrine containing solutions during ETHRANE anesthesia. ETHRANE anesthesia has been used in excision of pheochromocytoma in man without ventricular arrhythmias. On the basis of studies in patients anesthetized with ETHRANE and injected with epinephrine containing solutions to achieve hemostasis in a highly vascular area (transphenoidal surgery), it is recommended that 2 micrograms per kilogram (2μg/kg) of epinephrine may be injected subcutaneously over a 10 minute period. This may be repeated up to 3 times per hour.

Example: Up to 10 ml of 1:100,000 epinephrine containing solution (10μg/ml) may be injected subcutaneously over a 10 minute period in a 50 kilogram patient judged to have ordinary tolerance to epinephrine administration. No more than 30 ml of 1:100,000 epinephrine containing solution (10 μg/ml) should be administered to such a patient per hour. The concomitant administration of lidocaine enhances the safety of the use of epinephrine during ETHRANE anesthesia. This effect of lidocaine is dose related. All customary precautions in the use of vasoconstrictor substances should be observed.

Example Two: Alternatively, up to 20 ml of 1:200,000 epinephrine containing solution (5 μg/ml) may be substituted for 10 ml of 1:100,000 solution in the above example.

Muscle relaxation may be adequate for intra-abdominal operation at normal levels of anesthesia. Muscle relaxants may be used to achieve greater relaxation and all commonly used muscle relaxants are compatible with ETHRANE. The NONDEPOLARIZING MUSCLE RELAXANTS ARE POTENTIATED. In the normal 70 kg adult, 6 to 9 mg of d-tubocurarine or 1 to 1.5 mg of pancuronium will produce a 90 percent or greater depression of twitch height. Neostigmine does not reverse the direct effect of ETHRANE.

Biotransformation of ETHRANE in man results in low levels of serum fluoride ions averaging 15 mM/L. These levels are well below the 50 mM/L threshold level which can produce minimal renal damage in normal subjects; however, it is possible that these levels could result in damage in patients with severely impaired renal function or those undergoing renal transplantation. Depression of lymphocyte transformation does not follow prolonged ETHRANE anesthesia in man in the absence of surgery. Thus ETHRANE does not depress this aspect of the immune response.

INDICATIONS

ETHRANE (enflurane) may be used for induction and maintenance of general anesthesia. Adequate data have not been developed to establish its application in obstetrical anesthesia.

CONTRAINDICATIONS

Seizure disorders (see WARNINGS).

Known sensitivity to ETHRANE (enflurane) or other halogenated anesthetics.

WARNINGS

Increasing depth of anesthesia with ETHRANE (enflurane) may produce a change in the electroencephalogram characterized by high voltage, fast frequency, progressing through spike-dome complexes alternating with periods of electrical silence to frank seizure activity. The latter may or may not be associated with motor movement. Motor activity, when encountered, generally consists of twitching or "jerks" of various muscle groups; it is self-limiting and can be terminated by lowering the anesthetic concentration. This electroencephalographic pattern associated with deep anesthesia is exacerbated by low arterial carbon dioxide tension. A reduction in ventilation and anesthetic concentration usually suffices to eliminate seizure activity. Cerebral blood flow and metabolism studies in normal volunteers immediately following seizure activity show no evidence of cerebral hypoxia. Mental functions testing does not reveal any impairment of performance following prolonged ETHRANE anesthesia associated with or not associated with seizure activity.

Since levels of anesthesia may be altered easily and rapidly, only calibrated vaporizers which measure output with reasonable accuracy should be used. Hypotension and respiratory exchange can serve as a guide to anesthesia depth. Deep levels of anesthesia may produce marked hypotension and respiratory depression.

The action of nondepolarizing relaxants is augmented by ETHRANE. Less than the usual amounts of these drugs should be used. If the usual amounts of nondepolarizing relaxants are given, the time for recovery from myoneural blockade will be longer in the presence of ETHRANE than for other commonly used anesthetics.

Usage in Pregnancy: Safety in pregnancy has not been established. Reproduction studies have been performed in rats and rabbits, and there is no evidence of harm to the animal fetus. The relevance of these studies to the human is not known. Since there is no adequate experience in pregnant women who have received the drug, safety in pregnancy has not been established.

PRECAUTIONS

Bromsulfalein (BSP) retention is mildly elevated postoperatively in some cases. This may relate to the effect of surgery since prolonged anesthesia (5 to 7 hours) in human volunteers does not result in BSP elevation. There is some elevation of glucose and white blood count intraoperatively. Glucose elevation should be considered in diabetic patients. ETHRANE (enflurane) should be used with caution in patients who by virtue of medical or drug history could be considered more susceptible to cortical stimulation produced by this drug. As with other general anesthetics and some muscle relaxants, hyperpyrexia has been observed with the use of ETHRANE.

ADVERSE REACTIONS

1. Motor activity exemplified by movements of various muscle groups and/or seizures may be encountered with deep levels of ETHRANE (enflurane) anesthesia, or light levels with hypocapnia.
2. Hypotension and respiratory depression have been reported.
3. Arrhythmias, shivering, nausea, and vomiting have been reported.
4. Elevation of the white blood count has been observed.

DOSAGE AND ADMINISTRATION

The concentration of ETHRANE (enflurane) being delivered during anesthesia from a vaporizer should be known. This may be accomplished by using:

a) vaporizers calibrated specifically for ETHRANE.

b) vaporizers from which delivered flows can easily and readily be calculated.

Nothing is present in the agent to alter calibration or affect the operation characteristics of the vaporizer.

Preanesthetic Medication: Preanesthetic medication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by ETHRANE and the heart rate remains constant. The use of anticholinergic drugs is a matter of choice.

Induction: Induction may be achieved using ETHRANE alone with oxygen or in combination with oxygen-nitrous oxide mixtures. Under these conditions some excitement may be encountered. If excitement is to be avoided, a hypnotic dose of a short-acting barbiturate should be used to induce unconsciousness, followed by the ETHRANE mixture. In general, inspired concentrations of 2.0-4.5% ETHRANE produce surgical anesthesia in 7-10 minutes.

Maintenance: Surgical levels of anesthesia may be maintained with 0.5-3% ETHRANE. Maintenance concentrations should not exceed 3%. If added relaxation is required, supplemental doses of muscle relaxants may be used. Ventilation to maintain the tension of carbon dioxide in arterial blood in the 35-45 mm Hg range is preferred. Hyperventilation should be avoided in order to minimize possible CNS excitation.

The level of blood pressure during maintenance is an inverse function of ETHRANE concentration in the absence of other complication problems. Excessive decreases (unless related to hypovolemia) may be due to depth of anesthesia and in such instances should be corrected by lightening the level of anesthesia.

Overdosage: In the event of overdosage, or what may appear to be overdosage, the following action should be taken.

Stop drug administration; establish a clear airway and initiate assisted or controlled ventilation with pure oxygen.

PACKAGING

ETHRANE (enflurane) is packaged in 125 and 250 ml amber colored bottles.

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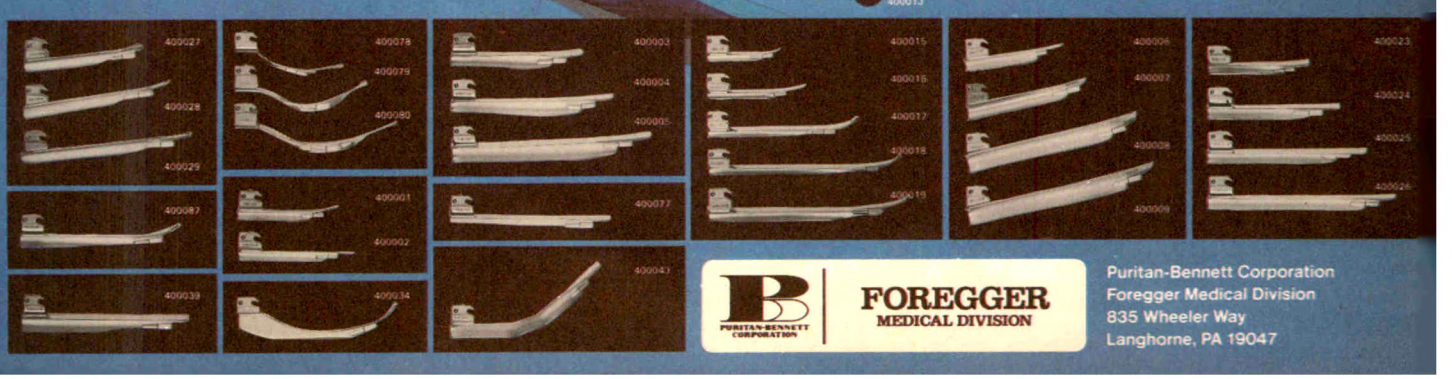
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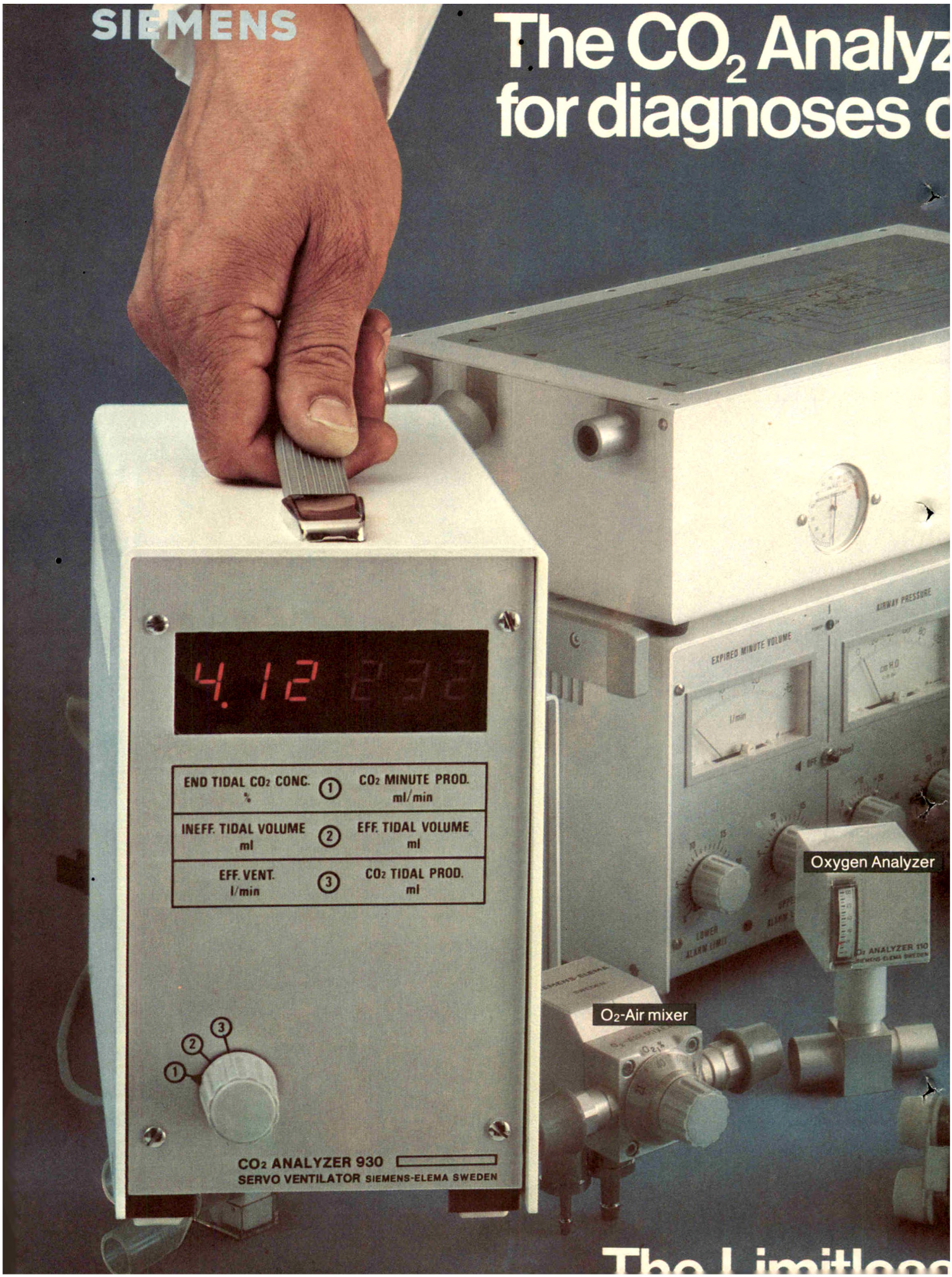




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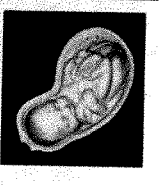
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Indications: Peripheral nerve block, infiltration, sympathetic block, caudal, or epidural block.

Contraindication: Marcaine is contraindicated in patients with known hypersensitivity to it.

Warnings: RESUSCITATIVE EQUIPMENT AND DRUGS SHOULD BE READILY AVAILABLE WHEN ANY LOCAL ANESTHETIC IS USED.

Usage in Pregnancy. Reproduction studies have been performed in rats and rabbits and there is no evidence of harm to the animal fetus. The relevance to the human is not known. Safe use in pregnant women other than those in labor has not been established.

Until further clinical experience is gained, paracervical block with Marcaine is not recommended. Fetal bradycardia frequently follows paracervical block with some amide-type local anesthetics and may be associated with fetal acidosis. Added risk appears to be present in prematurity, toxemia of pregnancy, and fetal distress.

The obstetrician is warned that severe persistent hypertension may occur after administration of certain oxytocic drugs, if vasopressors have already been used during labor (e.g., in the local anesthetic solution or to correct hypotension).

Solutions containing a vasoconstrictor, particularly epinephrine or norepinephrine, should be used with extreme caution in patients receiving monoamine oxidase (MAO) inhibitors or antidepressants of the triptyline or imipramine types, because severe, prolonged hypertension may result.

Local anesthetics which contain preservatives, i.e., those supplied in multiple dose vials, should not be used for caudal or epidural anesthesia.

Until further experience is gained in children younger than 12 years, administration of Marcaine in this age group is not recommended.

Precautions: The safety and effectiveness of local anesthetics depend upon proper dosage, correct technique, adequate precautions, and readiness for emergencies.

The lowest dosage that gives effective anesthesia should be used in order to avoid high plasma levels and serious systemic side effects. Injection of repeated doses of Marcaine may cause significant increase in blood levels with each additional dose, due to accumulation of the drug or its metabolites or due to slow metabolic degradation. Tolerance varies with the status of the patient. Debilitated, elderly patients and acutely ill patients should be given reduced doses commensurate with age and physical condition.

Solutions containing a vasoconstrictor should be used cautiously in areas with limited blood supply, in the presence of diseases that may adversely affect the patient's cardiovascular system, or in patients with peripheral vascular disease.

Marcaine should be used cautiously in persons with known drug allergies or sensitivities, particularly to the amide-type local anesthetics.

Serious dose-related cardiac arrhythmias may occur if preparations containing a vasoconstrictor such as epinephrine are employed in patients during or following the administration of chloroform, halothane, cyclopropane, trichloroethylene, or other related agents. In deciding whether to use these products concurrently in the same patient, the combined action of both agents upon the myocardium, the concentration and volume of vasoconstrictor used, and the time since injection, when applicable, should be taken into account.

Caution is advised in administration of repeat doses of Marcaine to patients with severe liver disease.

Adverse Reactions: Reactions to Marcaine are characteristic of those associated with other amide-type local anesthetics. A major cause of adverse reactions to this group of drugs is excessive plasma levels, which may be due to overdosage, inadvertent intravascular injection, or slow metabolic degradation.

Excessive plasma levels of the amide-type local anesthetics cause systemic reactions involving the central nervous system and the cardiovascular system. The *central nervous system effects* are characterized by excitation or depression. The first manifestation may be nervousness, dizziness, blurred vision, or tremors, followed by drowsiness, convulsions, unconsciousness, and possibly respiratory arrest. Since excitement may be transient or absent, the first manifestation may be drowsiness, sometimes merging into unconsciousness and respiratory arrest. Other central nervous system effects may be nausea, vomiting, chills, constriction of the pupils, or tinnitus. The *cardiovascular manifestations* of excessive plasma levels may include depression of the myocardium, blood pressure changes (usually hypotension), and cardiac arrest. In obstetrics, cases of fetal bradycardia have occurred (see Warnings).

Allergic reactions, which may be due to hypersensitivity, idiosyncrasy, or diminished tolerance, are characterized by cutaneous lesions (e.g., urticaria), edema, and other manifestations of allergy. Detection of sensitivity by skin testing is of doubtful value.

Reactions following epidural or caudal anesthesia also may include: high or total spinal block; urinary retention; fecal incontinence; loss of perineal sensation and sexual function; persistent analgesia, paresthesia, and paralysis of the lower extremities; headache and backache; and slowing of labor and increased incidence of forceps delivery.

Treatment of Reactions. Toxic effects of local anesthetics require symptomatic treatment; there is no specific cure. The physician should be prepared to maintain an airway and to support ventilation with oxygen and assisted or controlled respiration as required. Supportive treatment of the cardiovascular system includes intravenous fluids and, when appropriate, vasopressors (preferably those that stimulate the myocardium). Convulsions may be controlled with oxygen and intravenous administration, in small increments, of a barbiturate, as follows: preferably, an ultrashort-acting barbiturate such as thiopental or thiamylal; if this is not available, a short-acting barbiturate (e.g., secobarbital or pentobarbital) or diazepam. Intravenous barbiturates or anticonvulsant agents should only be administered by those familiar with their use.

References:

1. Ostheimer GW: Obstetrics and local anesthetics: Implications for the fetus and newborn. *Anesthesiology Review* 4:17-23, June 1977.
2. Scanlon JW: Obstetric anesthesia as a neonatal risk factor in normal labor and delivery. *Clinics in Perinatology* 1:465-482, 1974.
3. Scanlon JW, Ostheimer GW, Brown WU, et al: Neurobehavioral responses and drug concentrations in newborns after maternal epidural anesthesia with bupivacaine. *Anesthesiology* 45:400-405, 1976.

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0.25	2.5	—	1	—	—	—	—	—	—	—	—	—	—
0.25	2.5	1:200,000	1	0.5	.001	2	.0017	0.1	.5	.001	2	.0017	0.1
0.5	5.0	—	1	—	—	—	—	—	—	—	—	—	—
0.5	5.0	1:200,000	1	0.5	.001	2	.0017	0.1	.5	.001	2	.0017	0.1
0.75	7.5	—							—	—	—	—	—
0.75	7.5	1:200,000	Not Available in Vials						.5	.001	2	.0017	0.1

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*Solutions of Marcaine that contain epinephrine should not be autoclaved. Federal law prohibits dispensing without a prescription.

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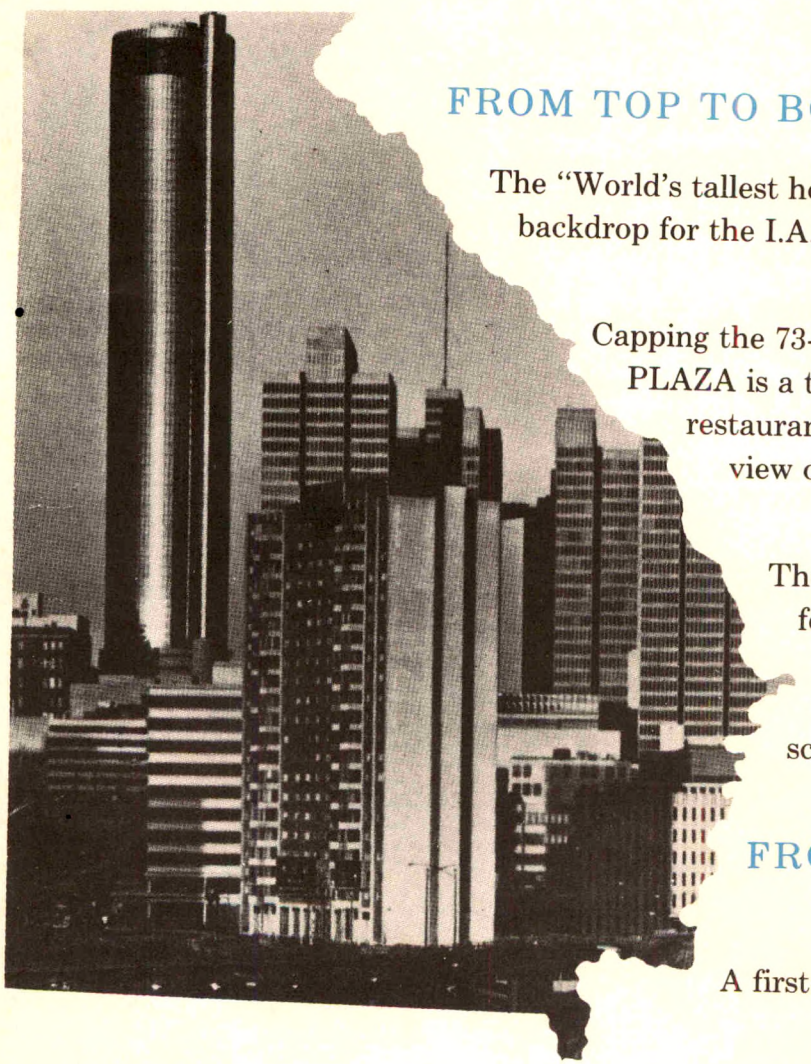
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INTERNATIONAL ANESTHESIA RESEARCH SOCIETY

55th Congress — March 8–12, 1981



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I.A.R.S. 55th CONGRESS—MEETING INFORMATION

SCHEDULE: Sunday, March 8th, 1981

Registration: 2–7 p.m.
Exhibits: 2–5 p.m.
Complimentary Informal Reception: 6–7 p.m.

NOTE: Registration will continue daily throughout the meeting.
Exhibits will continue through Tuesday, March 10th.

SCIENTIFIC PROGRAM: 8:30 a.m. to 5 p.m. Monday, March 9 through Wednesday, March 11
8:30 a.m. to 12 noon on Thursday, March 12th.

.... 66 Scientific papers
.... 15 Review Course Lectures
.... Panel on catastrophic illness
.... Seven "theme" luncheons (tickets to be sold at meeting)
.... Nineteenth Annual Baxter/Travenol Lecture—James E. Eckenhoff, M.D., D.Sc.: "Health Science Education, Responsibilities and Leadership"
.... Sixteenth Annual Becton, Dickinson and Company, Oscar Schwidetzky Memorial Lecture—C. Thorpe Ray, M.D.: "Voodoo Medicine"

PRE-REGISTRATION MATERIAL, HOTEL CARD, DAILY PROGRAM:

Complete meeting information will be mailed by mid-December to all I.A.R.S. members, associate members and educational members.

Non-I.A.R.S. members may receive material by writing or calling the Cleveland business office, 3645 Warrensville Center Rd., Cleveland, Ohio 44122. (216) 295-1124.

NOTE: Abstracts of the 66 scientific papers will be included in the final program booklet distributed at the meeting. A booklet including the 15 Review Course Lectures will be given to meeting attendees as part of their registration. After the meeting, the Review Course Booklet will be available for sale to others through the Cleveland business office.

REGISTRATION FEES:

	Paid by March 2	*Paid at Meeting*
IARS Members and Associate Members	$115	$125
IARS Educational Members	NO FEE	NO FEE
* New IARS Members and Associate Members	$150	$160
** New IARS Educational Members	$35/52	$35/52
Non Members	$165	$175
*** Non Members (residents, nurse trainees)	$ 25	$ 25

* — With membership application, includes dues for one year
** — With membership application, $35 for 2-yr. or $52 for 3-yr. membership
*** — With letter from program director

CONTINUING EDUCATION CREDITS:

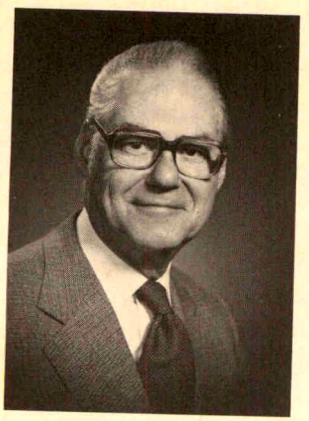
American Medical Association: This CME offering meets the criteria for 23 hours of Category 1 credit for the Physicians Recognition Award of the AMA.
American Association of Nurse Anesthetists: Prior approval pending for 23 AANA credits.

I.A.R.S. 55th CONGRESS DISTINGUISHED LECTURERS

NINETEENTH ANNUAL BAXTER/TRAVENOL LECTURE

Monday, March 9, 1981

"Health Science Education, Responsibilities and Leadership"



James E. Eckenhoff, M.D., D.Sc

Dean, and Professor of Anesthesia
Northwestern University Medical School
and
President, McGaw Medical Center of
Northwestern University
Chicago, Illinois

There is probably no one in the specialty better qualified than Doctor Eckenhoff to speak on the subject he has chosen. Distinguished educator and responsible leader, he literally "wrote the book" in anesthesia. To his colleagues throughout the world, he truly needs no further identification.

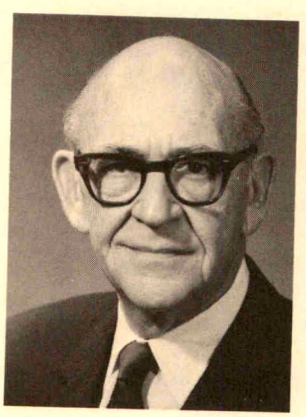
SIXTEENTH ANNUAL BECTON, DICKINSON AND COMPANY OSCAR SCHWIDETZKY MEMORIAL LECTURE

Tuesday, March 10, 1981

"Voodoo Medicine"

C. Thorpe Ray, M.D.

Professor and Chairman
Department of Medicine
Tulane University School of Medicine
and
Consultant Staff, Ochsner
Foundation Hospital and Touro Infirmary
New Orleans, Louisiana



Notwithstanding his firm dedication to conventional medicine—cardiovascular disease in particular—Doctor Ray's boundless curiosity has led him to explore the medical aspects of the ancient Voodoo religion. Even today, Voodoo medicine is a sorcery to be reckoned with in some parts of the world including the U.S., and as such this authoritative presentation will be of interest to anesthesiologists.

ANESTH ANALG
60:1-7, 1981

Causes of Death among Anesthesiologists: 1930–1946

Harry W. Linde, PhD,* Paul S. Mesnick, MD,† and Norbert J. Smith, PhB‡

LINDE, H. W., MESNICK, P. S., AND SMITH, N. J.: Causes of death among anesthesiologists: 1930–1946. Anesth Analg 1981;60:1–7.

The causes of death among anesthesiologists from 1930 through 1946 were determined and compared to the causes of death for contemporaneous physicians as well as anesthesiologists in later eras. Names of US white male anesthesiologists listed in the annual Directories of Anesthetists compiled by the International Anesthesia Research Society were searched for in the death files of the American Medical Association. Among those listed in the Directories 274 deaths were located. Causes were ascertained for 269 deaths and 259 causes were verified from death certificates. The leading causes of death of anesthesiologists and other physicians of the same era were cardiovascular-renal diseases and malignant neoplasms. The death rate from all causes was lower among anesthesiologists than among contemporaneous white men and other physicians. Death rates among anesthesiologists from 1930–1946 were similar to those among anesthesiologists in 1947–1956, but greater than those for 1957–1971. Among deaths from malignant neoplasms, those of the digestive organs were the most frequent and those of the respiratory tract the least. Anesthesiologists practicing in the earlier part of this century had lower death rates and they were less likely to die of malignant neoplasms than contemporaneous white men. The death rates for these anesthesiologists were similar to those for anesthesiologists during 1947–1956, but greater than rates observed for anesthesiologists during 1957–1971. This suggests that exposure to the fluorinated anesthetic agents introduced in the mid-1950s may not be an important health hazard.

Key Words: ANESTHESIOLOGISTS: causes of death.

OCCUPATIONAL exposure to the vapors of inhalation anesthetics could be a health hazard and thus influence the mortality experience of anesthesiologists. (The word anesthesiologist came into use in the 1940s to describe physicians (MD) who gave anesthesia and to distinguish them from nonmedical anesthetists such as nurses. It is used here to describe all physician-anesthetists regardless of their period of practice.) The agents to which anesthesiologists have been exposed have changed over the years. In the early years, ether, nitrous oxide, and chloroform predominated. Chloroform, which has been shown to be a carcinogen in animals (1), was used during the latter half of the 19th century and into the 20th century. With the recognition of its side effects, and with the introduction of newer and safer drugs, the use of chloroform declined, so that by the mid-20th century, it was rarely used for anesthesia. If we consider anesthesiologists dying between 1930 and 1946 to average 65 years of age and 40 years of practice, these anesthesiologists would have given anesthetics between 1890–1946, during the later period of chloroform use. If chloroform causes long-term toxic effects, e.g., carcinogenesis, then mortality statistics for a large group of anesthesiologists should reflect this toxicity.

This study was undertaken to identify a population of anesthesiologists, to determine the causes of death of those who died during the years 1930–1946, and to compare these mortality statistics with those of other groups.

Methods

White male anesthesiologists living in the United States and listed in the annual Directory of Anesthetists of the International Anesthesia Research Society (IARS) were chosen as the population to be studied

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Supported in part by Health Effects Research Laboratory Grant R805473-01, US Environmental Protection Agency.

Received from the Department of Anesthesia, Northwestern University Medical School, McGaw Medical Center, 303 East Chicago Avenue, Chicago, Illinois 60611, and Statistical Bureau, Metropolitan Life Insurance Co. Accepted for publication September 15, 1980. Presented, in part, at the Annual Meeting of the American Society of Anesthesiologists, October 20–24, 1979, San Francisco, California (abstract appears in Anesthesiology 1979;51:S338).

Reprint requests to Dr. Linde.

(2-6). The population was limited to white men by eliminating those with a given name of the female gender, or those who were listed as women or nonwhite in the American Medical Association death files or on the death certificate. The total population of male anesthesiologists was obtained by counting names that appeared in the IARS directories for 1930, 1935, 1938, 1941, and 1948. The age distribution of the population for these years was obtained by selecting, at random, a 5% sample of names from each of these directories. The year of birth for each individual was obtained from American Medical Directories (7-10). Ages were calculated and the percentage falling within each 10-year age group, starting at age 25, was determined. Numbers of anesthesiologists in each age group were enumerated for each year listed above. The population and age distribution for intermediate years were obtained by linear interpolation. The names of male anesthesiologists appearing in the IARS directories for the years 1930, 1935, 1938, and 1941 were searched for in the death files of the American Medical Association.

The directories of anesthetists were not membership lists of the IARS, rather they were lists of anesthesiologists, regardless of affiliation. Each directory solicited from its readers, names of physicians practicing anesthesia. These directories are the most complete lists of anesthesiologists available for the period and thus provide a sound basis for selection of a study population.

The names of anesthesiologists who died between January 1, 1930, and December 31, 1946, were recorded on index cards along with the date and place of death, age, cause of death, and last known address, when available. Copies of death certificates were obtained from the registrars of vital statistics of the various states and the City of New York to ascertain or verify the cause of death. These data make up the observed causes of death of male anesthesiologists, 1930-1946.

The death rates for selected causes observed in this population were compared to several other populations to evaluate possible differences in the causes of death. Two forms of comparison of death rates were used, the proportional death rate and the mortality ratio. The proportional death rate is the percentage of the total deaths attributable to a given cause. The mortality ratio is the ratio of deaths occurring in the study population and deaths expected to occur in a comparison population of similar age distribution. The four populations chosen for comparison of mortality ratios were: (*a*) US white men, 1930-1946 (11, 12); (*b*) US white male physicians, 1938-1942 (13, 14); (*c*) Metropolitan Life Insurance Company standard ordinary life insurance policyholders, 1966; and (4) members of the American Society of Anesthesiologists, 1947-1956, 1957-1966, and 1967-1972 (15, 16, and unpublished data of D. L. Bruce, K. A. Eide, H. W. Linde, and J. E. Eckenhoff). Proportional death rate comparisons were made only with US physicians, 1938-1942.

Expected death rates for US white men during 1930-1946 were calculated from US vital statistics rates (11) by averaging death rates for the years 1930, 1933, 1937, 1940, 1943, and 1946 for each 10-year age group between 25 and 84. Expected death rates for digestive and respiratory system neoplasms and leukemia and aleukemia were only available for 1940 (12). These expected death rates were adjusted to the age distribution of the anesthesiologist population. For each 10-year age group, the number of anesthesiologists at risk of death was multiplied by the expected US white male death rate for that age group to give the number of expected deaths of anesthesiologists. These expected deaths were summed for ages 25 to 84 and compared with the observed number of deaths. Expected death rates for male physicians (13, 14) and for standard policyholders of the Metropolitan Life Insurance Company were also age-adjusted to the 1930-1946 anesthesiologist population. These policyholder death rates were also used by Bruce et al (15, 16) in their studies of causes of death of anesthesiologists. Mortality ratios for anesthesiologists compared to contemporaneous white men for 1947-1956 and 1957-1966 were obtained from unpublished data of Bruce et al. Causes of death were classified according to the fifth revision of the International List of Causes of Death (17) for comparison with contemporaneous vital statistics rates and according to the seventh revision (18) for comparison with rates for life insurance policyholders and the data of Bruce et al (15, 16). Deaths coded according to the fifth and earlier revisions of the International List of Causes of Death did not include Hodgkin's disease or leukemia as malignant neoplasms and available vital statistics rates do not include these diseases with malignancies.

The standard deviation of a mortality ratio is approximately equal to mortality ratio/$\sqrt{\text{number of deaths}}$ if a normal distribution can be assumed for the number of deaths or the death rate. This assumption is reasonable when the number of deaths is greater than approximately 20 (19, 20). The 95% confidence limits equal 2 SD. These 95% confi-

dence limits refer to biologic randomness and do not include possible errors in the conduct of the study.

This investigation was reviewed and approved by the Institutional Review Board of Northwestern University.

Results

The names of 274 white male anesthesiologists, who were listed in IARS directories of anesthetists, and who died between January 1, 1930 and December 31, 1946, were located. Copies of death certificates were obtained for 259 of these deaths. In 15 instances, death certificates were not available. Overall, 259 causes of death were obtained from death certificates, 10 from the American Medical Association files, and five remain unknown.

The numbers and age distribution of the anesthesiologists who were included in this study are shown in Table 1. The deaths occurring among these anesthesiologists over the period 1930–1946 are given by cause and age at death in Table 2. In Table 3, the proportional death rates of this group of anesthesiologists are compared to US physicians during 1938–1942 (13, 14). In Table 4, the age-adjusted mortality ratios observed in the study population to those expected among contemporaneous US white men are shown; 95% confidence limits are given for the major causes of death. For comparison, similar mortality ratios are shown for anesthesiologists in the subsequent two decades and for US physicians during 1938–1942.

Age-adjusted mortality ratios were also derived by comparing the subjects of this study to those of male standard ordinary policyholders of the Metropolitan Life Insurance Company (Table 5).

The leading causes of death among anesthesiologists during 1930–1946 were cardiovascular-renal diseases and malignant neoplasms. The same was true for all physicians of the same era. The comparatively high rates for suicide and the low rates for respiratory malignancies are notable. Infectious diseases also claimed a high proportion of lives.

The observed mortality ratios suggest that the death rate for anesthesiologists in this study was lower than that for US white men for most causes. Mortality from all malignant neoplasms, as well as those of the individual systems, was lower than among the white male population, especially for respiratory malignancies.

The death rate for all causes in the study population

TABLE 1

White Male Anesthesiologist Population and Age Distribution

Age range	Year (population)				
	1930 (1119)	1935 (1099)	1938 (1418)	1941 (1634)	1948 (1972)
yr			%		
25–34	10.4	11.5	11.8	16.5	9.4
35–44	32.3	34.4	32.9	28.2	33.0
45–54	31.8	29.5	28.9	21.2	31.1
55–64	20.9	21.3	15.8	22.4	21.7
65–74	4.5	3.3	10.5	10.6	3.8
75–up	0.0	0.0	0.0	1.2	0.9

TABLE 2

Death of White Male Anesthesiologists, 1930–1946, by Age and Cause*

Cause of death	Age (yr)						Total
	25–34	35–44	45–54	55–64	65–74	75–up	
All causes	9	26	52	93	64	30	274
Cardiovascular renal	1	10	29	62	51	20	173
Vascular lesions of the CNS	0	2	7	10	13	3	35
Diseases of heart	1	7	19	47	34	11	119
Chronic and unspecified nephritis	0	0	2	4	1	3	10
Malignant neoplasms	4	1	4	11	8	3	31
Digestive	2	1	1	8	5	1	18
Respiratory	0	0	0	1	0	0	1
Leukemia and aleukemia	1	0	0	0	0	0	1
Lymphosarcoma	0	0	3	0	0	0	3
Accidents	0	2	4	2	0	2	10
Suicides	0	2	4	4	0	0	10
All other causes	4	11	11	14	5	5	50
Infection	4	6	5	2	2	1	20
Cause unknown	0	0	2	1	1	1	5

* Total deaths listed by major category (italic) and specific causes (roman); deaths from specific causes are included in the major categories. Sum of the deaths in each major category ("All causes") equals the "Total."

was similar to that of life insurance policyholders; however, rates for certain causes differed. Death rates from suicides and vascular lesions of the central nervous system in the study population were more than twice that of the policyholders. Cancer death rates were low, except for deaths due to malignancies of the digestive organs. Respiratory cancer rates were especially low among anesthesiologists.

Discussion

Sources of Information

Three sets of records form the basis of this investigation, the directories of anesthetists of the IARS, the death files of the American Medical Association, and vital statistics records of the states and New York City. The records of the American Society of Anesthesiologists and predecessor societies were also examined. These latter records, although providing some information on deaths, are too incomplete during the era under study to be useful in this study.

The American Medical Association (AMA) published the American Medical Directory, *A Register of Legally Qualified Physicians of the United States*. The Directory was published at 2- or 3-year intervals from 1906 through 1942 and then again in 1950. To prepare this directory, the AMA maintained a file card for each physician in the United States. Medical school graduation lists, information from state boards of registration in medicine, medical societies, etc were the sources used to prepare this file. Physicians were asked routinely to provide information to update their listings. The file cards usually contain the physician's name, date of birth, sex, race if other than white,

TABLE 3

Proportional Death Rates of Anesthesiologists and US Physicians*

Cause of death	Anesthesiologists 1930–1946†	US physicians 1938–1942‡
	%	
Cardiovascular-renal diseases	63.1	59.8
Vascular lesions of the CNS	12.8	10.8
Diseases of the heart	43.4	40.7
Chronic and unspecified nephritis	3.6	5.9
Malignant neoplasms	11.3	10.3
Digestive	6.6	4.3
Respiratory	0.4	1.0
Leukemia, aleukemia	0.4	0.6
Lymphoid, reticuloendothelial system	1.1	—§
Accidents	3.6	4.6
Suicides	3.6	1.9
All other causes	18.2	23.4
Infection	7.3	—§
Cause unknown	1.8	1.2

* Total deaths listed by major category (italic) and specific causes (roman); percent of deaths from specific causes are included in the major categories.

† This study.

‡ US white male physicians, 1938–1942 (13, 14).

§ Not available.

TABLE 4

Mortality Ratios of Anesthesiologists and US Physicians to US White Men*

Cause of death	Anesthesiologists 1930–1946†	Anesthesiologists 1947–1956‡	Anesthesiologists 1957–1966‡	US physicians 1938–1942§
All causes	0.76 ± 0.092	0.74	0.51	1.02
Cardiovascular-renal	1.01 ± 0.154	1.07	0.54	1.12
Vascular lesions of CNS	1.25 ± 0.422	0.75	0.65	1.20
Disease of heart	1.06 ± 0.194	1.39	0.60	1.18
Chronic and unspecified nephritis	0.40	1.03	2.16	—‖
Malignant neoplasms	0.69 ± 0.248	0.59	0.54	0.84
Digestive	0.74¶	—‖	0.68	—‖
Respiratory	0.18¶	—‖	0.32	—‖
Leukemia and aleukemia	0.67¶	1.18	0.83	1.75
Accidents	0.34	0.22	0.49	0.71
Suicide	1.03	1.22	1.44	1.04
All other causes	0.46	0.34	0.22	—‖

* Total deaths listed by major category (italic) and specific causes (roman); age-adjusted ratios of observed deaths among anesthesiologists and other physicians to number expected among contemporaneous US white men, ±95% confidence limits shown where number of deaths are sufficient.

† This study.

‡ D. L. Bruce, and colleagues, unpublished data.

§ US male physicians (13, 14).

‖ Data not available.

¶ Ratios to US white male rates for 1940 only (12).

TABLE 5

Mortality Ratios of Anesthesiologists to Life Insurance Policyholders*

Cause of death	1930–1946†	1947–1956‡	1957–1966‡	1967–1971‡
All causes	1.09 ± 0.132	1.04	0.60	0.75
Cardiovascular-renal	1.22 ± 0.186	1.44	0.61	0.81
Vascular lesions of CNS	2.16 ± 0.730	1.30	0.77	0.89
Disease of heart	1.12 ± 0.205	1.48	0.62	0.85
Malignant neoplasms	0.59 ± 0.212	0.60	0.56	0.64
Digestive	1.13	0.62	0.64	0.71
Respiratory	0.06	0.11	0.30	0.48
Leukemia and aleukemia	0.45	1.33	0.91	0.40
Accidents	0.89	0.41	0.76	0.80
Suicides	2.78	2.20	2.86	2.98
All other causes	1.20	0.58	0.30	0.36

* Total deaths listed by major category (italic) and specific causes (roman); age-adjusted ratio of observed deaths among anesthesiologists to number expected among male standard ordinary policyholders of Metropolitan Life Insurance Company, 1966, ±95% confidence limits shown where number of deaths are sufficient.

† This study.

‡ American Society of Anesthesiologists members (16).

name of medical school, date of graduation, current and previous addresses, and other information. On notification of the death of a physician, the card was removed from the active file and placed in a death file. When removed from the active file, the date, place and often cause of death, and the source of this information were added to the card. The obituary from the *Journal of the American Medical Association* was often pasted to the card. Notifications of death were received from state boards, registrars of vital statistics, medical societies, colleagues, and families of the deceased. These records of the AMA are the most complete records available for physicians of the period. Short of searching the vital statistics records of each state and New York City for the 17-year period, they provide the best source of information available for this investigation.

Copies of death certificates were obtained by mail request from vital statistics offices.

Mortality

Deaths occurring among anesthesiologists were examined by the proportional death rate and by mortality ratios. Two standards were used to compute mortality ratios: expected deaths of contemporaneous US white men and expected deaths of life insurance policyholders during 1966. These latter comparisons were made because the desired vital statistics rates were available in appropriate detail (i.e., by age, race, sex, and cause) and to allow further comparison with other physicians and with anesthesiologists in later time periods.

The proportional death rate is a useful tool to examine the relative importance of different diseases in causing death. The proportional rate for a given cause, however, is affected not only by changes in the number of deaths from the cause, but also by changes in numbers of deaths from other causes.

Two comparison populations were selected for calculation of mortality ratios, US white men during 1930–1946, and male life insurance policyholders during 1966. Contemporary white men and anesthesiologists were exposed to the same environment (physical, chemical, biologic, etc). Inasmuch as anesthesiologists were of a higher socioeconomic class, they probably had superior nutrition, health care, and living conditions. This in turn could have contributed to lower death rates. Vital statistics by socioeconomic class for that time period are not available. The life insurance policyholders were generally employed and of somewhat higher socioeconomic class than US white men, but were not contemporaneous with the anesthesiologists studied. The use of the 1966 policyholder death rates allowed us, however, to make comparisons with anesthesiologists through 1971.

The three leading causes of death among anesthesiologists—diseases of the heart, vascular lesions of the central nervous system, and cancer—were the same as those for all physicians as a group living at the same time (13, 14). Anesthesiologists had nearly double the proportion of suicides, however. Data for physicians include those for anesthesiologists; however, this introduces little bias since less than 1% of all US physicians were anesthesiologists during the study period (2–6, 10).

When compared to contemporaneous nonphysician white men, mortality ratios of anesthesiologists from all causes were only three fourths of the ratios expected, about the same ratio as the expected for cardiovascular-renal diseases, and lower than the expected ratio for cancer, accidental death, and the residual (all other) causes. The lower mortality from cancer could have been due to earlier detection and treatment. The residual category includes some causes that were more prevalent in lower socioeconomic classes (e.g., tuberculosis). In contrast to anesthesiologists, other physicians of the same era experienced mortality similar to the white male population (13, 14). The reason for the difference in mortality from all causes is not clear from the available data, although cancer and accidental death ratios were lower for anesthesiologists.

When compared to policyholders, mortality ratios for anesthesiologists in this study were similar to those for anesthesiologists during 1947–1956, but were greater than those for anesthesiologists during 1957–1966 and 1967–1971. This pattern prevails for the cardiovascular-renal diseases combined, although vascular lesions of the central nervous system are a more prominent cause, and diseases of the heart less, in the study group years than in the next decade.

Overall cancer death ratios have changed little for anesthesiologists over the years, although the mortality ratios for digestive organ neoplasms were greatest during the study period. The respiratory system neoplasm mortality ratio increased steadily from 1930–1946 through 1967–1971, but it never reached one half of the expected rate.

Mortality ratios for neoplasms of the digestive organs decreased among anesthesiologists after 1930–1946, especially when compared to expected rates for policyholders. It is difficult to ascribe significance to this difference since small numbers of deaths are

involved and because the mortality ratio to contemporaneous white men is low. The two types of malignant tumors that were observed in rodents fed chloroform, i.e., kidney epithelial tumors and hepatocellular carcinoma, were not a prominent cause of death of anesthesiologists (1). In the study group of anesthesiologists there was one death from cancer of each of these organs, giving a proportional death rate of 0.4% for each. Comparison vital statistics are not available to calculate mortality ratios. Respiratory system neoplasm deaths were, in contrast, remarkably low during 1930–1946 and remained low for anesthesiologists through 1967–1971. The low rate observed by Bruce et al (15, 16) in the 1947–1966 study led them to investigate the cigarette smoking habits of anesthesiologists. They found no difference between anesthesiologists and the general population in their 1967–1971 study (21). Since the hazards of cigarette smoking were less well recognized before 1946, and since cigarettes were advertised in medical journals, it is unlikely that anesthesiologists smoked less than their white male contemporaries.

It was not possible to calculate mortality ratios to US white men for lymphosarcoma since this cause of death was not considered separately in vital statistics rates before 1948. Data are not available for this cause of death among the life insurance policyholders.

Suicide

Bruce et al (15, 16) found a high incidence of suicide among anesthesiologists as compared to white men or policyholders. This does not appear to be true for anesthesiologists during 1930–1946. Although their suicide rate was high when compared to white men or policyholders in later years, it was nearly equal to contemporaneous white men and physicians. During the depression years (1930–1940), the white male death rate for suicide was high (11).

Whereas the anesthesiologists considered here were listed as medical anesthetists in the IARS directories it is impossible to ascertain how much of their time was devoted to anesthesia; their exposure to anesthetics is therefore difficult to estimate. Full-time medical specialization was much less common in those years and it is likely that many were part-time anesthesiologists. Nonetheless, their mortality experience differs from contemporaneous physicians as a whole and is similar to that of anesthesiologists in the subsequent decade who must have experienced similar anesthetic exposure.

Lew (20) has studied deaths of anesthesiologists from 1954–1976, using the membership lists of the American Society of Anesthesiologists as the population. For calculation of mortality ratios, he compared anesthesiologists to US physicians. He also subdivided his population to examine those practicing before and after the introduction of halothane. He found that the major causes of death in both groups were cardiovascular disease and cancer and both groups also had a high suicide rate. In both, Lew's findings parallel those of this study. The mortality ratio found by Lew for deaths from all causes during 1954–1976 does not differ from that for anesthesiologists during 1930–1946. He observed a downward trend in mortality ratios over time, an observation consistent with our findings when compared to those of Bruce et al (15, 16). Lew concluded that there was no increase in overall mortality or mortality from cancer subsequent to the introduction of halothane. This is also consistent with our conclusions.

Conclusions

The practice of anesthesiology in the early part of the 20th century did not increase risk of death of its practitioners. It appears that occupational exposure to the anesthetic vapors then in use did not have adverse health effects, at least as reflected in mortality statistics. Death rates for anesthesiologists were similar in the periods 1930–1946 and 1947–1956, before the introduction of the fluorinated anesthetic agents. Death rates decreased over the period 1957–1976 after the introduction of these agents. This suggests that the fluorinated agents do not adversely effect the health of anesthesiologists, although 20 years may be insufficient time for such effects to become manifest in death rates.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the assistance of Ms. Victoria Bigelow of the American Medical Association, Mr. Patrick Sim of the Wood Library and Museum of the American Society of Anesthesiologists, David L. Bruce, MD, Thomas H. Seldon MD, Ms. Karen McGary, Ms. Shelia Brown, Ms. Rita Schwimmer, and the vital statisticians of the United States.

REFERENCES

1. National Institutes of Health. Report on carcinogenesis bioassay of chloroform. Bethesda, MD: Carcinogenesis Program, Division of Cancer Cause and Prevention, National Cancer Institute, National Institutes of Health, March 1, 1976.
2. International Anesthesia Research Society. Directory of anesthetists 1930. Avon Lake, OH: International Anesthesia Research Society, 1930.
3. International Anesthesia Research Society. Directory of anesthetists 1935. Rocky River, OH: International Anesthesia Research Society, 1935.

4. International Anesthesia Research Society. Directory of anesthetists 1938. Rocky River, OH: International Anesthesia Research Society, 1938.
5. International Anesthesia Research Society. Directory of anesthetists 1941. Rocky River, OH: International Anesthesia Research Society, 1941.
6. International Anesthesia Research Society. Directory of anesthetists 1948. Rocky River, OH: International Anesthesia Research Society, 1948.
7. American Medical Association. American medical directory. 12th ed. Chicago: American Medical Association, 1931.
8. American Medical Association. American medical directory. 14th ed. Chicago: American Medical Association, 1936.
9. American Medical Association. American medical directory. 17th ed. Chicago: American Medical Association, 1942.
10. American Medical Association. American medical directory. 18th ed. Chicago: American Medical Association, 1950.
11. US Department of Health, Education and Welfare, Public Health Service, National Office of Vital Statistics. Death rates by age, race and sex, 1900–1953. Vital Statistics-Special Reports; 43:1956.
12. Grove RD, Hetzel AM. Vital statistics rates in the United States, 1940–1960. Washington, DC: US Department of Health, Education and Welfare, Public Health Service, National Center for Health Statistics, 1968.
13. Dublin LI, Spiegelman M. The longevity and mortality of American physicians. JAMA 1947;134:1211–1215.
14. Dublin LI, Spiegelman M, Leland, RG. Longevity and mortality of physicians. Postgrad Med 1947;2:188–202.
15. Bruce DL, Eide KA, Linde HW, Eckenhoff JE. Causes of death among anesthesiologists: a 20-year survey. Anesthesiology 1968;29:565–569.
16. Bruce DL, Eide KA, Smith NJ, Seltzer F, Dykes MHM. A prospective survey of anesthesiologist mortality. Anesthesiology 1974;41:71–74.
17. US Department of Commerce, Bureau of the Census. Manual of the international list of causes of death. Based on the 5th decennial revision by the International Commission, Paris, October 1938. Washington, DC: United States Government Printing Office, 1940.
18. World Health Organization. Manual of the international statistical classification of diseases, injuries, and causes of death. 7th revision. Geneva: World Health Organization, 1957.
19. Gershenson H. Measurement of mortality. Chicago: Society of Actuaries, 1961.
20. Lew EA. Mortality experience among anesthesiologists, 1954–1976. Anesthesiology 1979;51:195–199.
21. Bruce DL, Eide KA, Smith NJ, Seltzer F, Dykes MHM. Characteristics of the American Society of Anesthesiologists' membership 1967–1971. Anesthesiology 1974;41:67–70.

Epidural versus General Anesthesia for Total Hip Arthroplasty

Sixty consenting patients undergoing total hip replacement received by random assignment either epidural analgesia with bupivacaine 0.75% or general anesthesia with thiopentone, fentanyl, pancuronium, N_2O/O_2. Before surgery the patients were of equal physical status with normal and similar laboratory values. All patients were mentally normal for their age. On the first postoperative day, the general anesthesia group had a significantly lower Pa_{O_2} than the epidural group ($p < 0.025$). Pa_{O_2} in the general anesthesia group was significantly lower than the preoperative values on the first and third postoperative days ($p < 0.001$ and $p < 0.01$, respectively). None of the 29 patients in the epidural group but seven of 31 patients in the general anesthesia group had significant mental changes after surgery ($p < 0.01$). Five of these patients still had mental changes that reduced their quality of life several months later. In the general anesthesia group, one patient died from an acute myocardial infarction. Low postoperative Pa_{O_2} might have contributed to this death. Two patients in the epidural group had symptoms of pulmonary embolism after surgery. Thus elderly patients appear to do better after hip replacement with less deterioration of cerebral and pulmonary functions when given epidural analgesia than when surgery is performed under general anesthesia. *(Hole A, Terjesen T, Breivik H: Epidural versus general anaesthesia for total hip arthroplasty in elderly patients. Acta Anaesth Scand 1980;24:279–287)*

ANESTH ANALG
60:8-11, 1981

Pharmacokinetics of High-Dose Meperidine in Surgical Patients

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KOSKA, A. J., III, KRAMER, W. G., ROMAGNOLI, A., KEATS, A. S., AND SABAWALA, P. B.: Pharmacokinetics of high-dose meperidine in surgical patients. Anesth Analg 1981;60:8-11.

Intravenous meperidine is used during surgical procedures at doses up to 5 mg/kg. At the commonly used analgesic intravenous doses of 50 to 100 mg (0.7 to 1.4 mg/kg), the drug exhibits two-compartment open model pharmacokinetics, with elimination primarily by hepatic metabolism (>90% of a dose). Drugs eliminated to a large extent by metabolism may, however, be subject to dose-dependent kinetics. We therefore studied the pharmacokinetics of meperidine when administered as 5 mg/kg IV bolus injections in surgical patients undergoing corrective vascular surgery involving the lower part of the abdominal aorta and the femoral and popliteal arteries. Serial blood samples were collected over 10 hours and plasma meperidine concentrations were determined by a gas chromatographic assay. Semilogarithmic plots of plasma meperidine concentration vs time were biphasic; however, the curves' irregularities during the time the arterial vessels were clamped suggest that the data should be analyzed in a model-independent manner. These irregularities suggest that the disposition of meperidine is altered during the clamping period and that these alterations are quickly reversed following removal of the clamp. Our findings agree with those reported in the literature following a total dose of 50 mg (half-life average 4.4 hours, total plasma clearance 10.4 ml/min/kg, and apparent volume of distribution 3.74 L/kg). The present results thus indicate that although meperidine is eliminated to a large extent by metabolism, the processes involved are apparently not saturated at doses 7 times greater than normal.

Key Words: ANALGESICS: meperidine; PHARMACOKINETICS: meperidine.

MEPERIDINE is a narcotic analgesic commonly used as an adjunct to anesthesia for major surgical procedures in doses of 2 to 5 mg/kg of body weight. The pharmacokinetics of meperidine have been studied in normal volunteers and surgical patients with doses of 50 mg to 100 mg (0.7 to 1.4 mg/kg) (1-3). In the latter studies, meperidine was found to exhibit pharmacokinetics indicating a two-compartment open model, with elimination primarily by hepatic metabolism. Ninety percent of an intravenously administered dose of meperidine is said to be eliminated following demethylation to normeperidine and hydrolysis to meperidinic acid (4).

Drugs eliminated to a large extent by metabolism may be subject to dose-dependent kinetics, particularly after a 7-fold increase in the dose. This paper reports the results of a study of meperidine disposition in surgical patients at doses of 5 mg/kg.

Methods and Materials

Six patients undergoing operations for peripheral vascular disease, not requiring cardiopulmonary bypass, were selected as subjects. Each patient was within the range of the normal ratio between weight and height, had no known illness other than that being treated by the surgical procedure, and had normal hepatic and renal function as determined by routine laboratory procedures. Pertinent patient data are shown in Table 1. This study was approved by appropriate institutional review committees and signed informed consent was obtained from each patient before admission to the study.

Patients received no meperidine for at least 24 hours before surgery. Following induction of anesthesia with sodium thiopental, 3 mg/kg, and diazepam,

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Received from the Department of Pharmaceutics, College of Pharmacy, University of Houston, Texas Medical Center, Houston, Texas and the Department of Cardiovascular Anesthesiology, Texas Heart Institute, Houston, Texas. Accepted for publication September 22, 1980.
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0.3 mg/kg, the administration of enflurane 1% was started and 5 mg/kg of meperidine was administered intravenously as rapidly as it was tolerated without production of arterial hypotension. Enflurane was discontinued following induction and only used intermittantly for control of hypertension during the surgical procedure. A 50% mixture of nitrous oxide in oxygen was administered throughout the surgical procedure by intermittent positive pressure ventilation. EEG, ECG, and arterial blood pressure were continuously monitored by oscilloscope. Blood pH, gas tensions, and electrolyte levels were measured at regular intervals. Blood samples were drawn from the arterial line immediately before and 5, 10, 15, 20, 25, 45, 60, 90, 120, 150, 180, 240, 300, 360, 480, and 600 minutes after administration of meperidine. Samples were collected in evacuated containers containing sodium heparin and centrifuged at 3000 rpm for 5 minutes; then plasma was removed and frozen until assay.

Plasma samples were assayed for meperidine using a gas liquid chromatographic procedure. For analysis, 1.0 ml of either a plasma sample or plasma standard was placed into a screw-capped culture tube along with 1.0 ml of internal standard (lidocaine-HCl, 2 μg/ml). Trichloroacetic acid (20%, 0.4 ml) was added to precipitate protein, the tube was put through a vortex, and then centrifuged for 3 minutes. The supernatant fluid was decanted to a clean tube; 0.4 ml of 50% NaOH and 100 μl of benzene were added; the tube was put through a vortex and then centrifuged to separate the phases. A 5-μl aliquot of the benzene phase was injected into the gas chromatograph. The analyses were performed on a gas chromatograph (model 5736A, Hewlett-Packard, Waltham, MA) equipped with a nitrogen-phosphorus selective detector. The gas chromatograph was fitted with a 6 ft x ¼ in glass column packed with 3% OV-17 on Gas Chrom Q (Applied Science Labs, Inc, State College, PA). Carrier gas (helium) flow rate was maintained at 40 ml/min, air at 50 ml/min, and hydrogen at 3 ml/min. The injection port, column, and detector were kept at 250, 190, and 250 C, respectively. Chromatograms were recorded and areas under peaks of interest integrated by a Hewlett-Packard 3385A Automation System. Quantification was done using the ratio of the area under the meperidine peak to that of the internal standard.

TABLE 1
Patient Data

Patient	Sex	Weight	Surface area	Surgical procedure
		kg	m^2	
1	M	76	1.92	Abdominal aortic aneurysm
2	M	83	1.92	Abdominal aortic aneurysm
3	F	55	1.55	Femoral popliteal bypass
4	M	91	2.07	Femoral popliteal bypass
5	M	81	2.01	Femoral popliteal bypass
6	M	65	1.63	Femoral popliteal bypass

Representative chromatograms of a standard plasma and a patient plasma are shown in Fig 1. It should be noted that this method will separate the metabolite normeperidine from the parent compound, although no normeperidine was seen in any patient sample.

Semilogarithmic plots of plasma meperidine concentration vs time showed biphasic decay, indicative of two-compartment pharmacokinetics. However, the curves appeared to deviate somewhat during the time the arterial vessel was clamped during the surgical procedure (Fig 2). Consequently, the data were analyzed in a model-independent manner rather than adhering to strict two-compartment methods.

Plasma half-life ($t_{1/2}$) was calculated from

$$t_{1/2} = 0.693/\beta \quad (1)$$

where β is the negative slope of the terminal log-

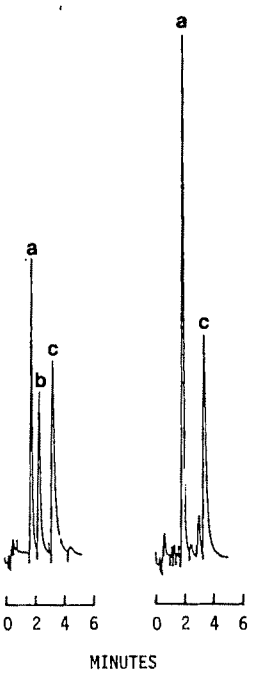


FIG 1. Representative chromatograms for meperidine (a), normeperidine (b), and lidocaine (c) from a standard plasma (left) and a patient sample (right). Standard plasma contained 2.5 μg/ml each of meperidine and normeperidine. Retention times for meperidine, normeperidine, and lidocaine were 2.4, 3.2, and 4.6 minutes, respectively.

linear segment of the concentration time curve. All slopes were calculated using linear regression.

Total plasma clearance (CL_T) was calculated according to

$$CL_T = \frac{dose}{AUC} \quad (2)$$

where AUC is the area under plasma concentration-time curve from zero to infinity. Areas were calculated using the trapezoidal method from zero to the last data point and by extrapolation from the last point to infinity. The apparent volume of distribution (Vd_β), was calculated from

$$Vd_\beta = CL_T/\beta \quad (3)$$

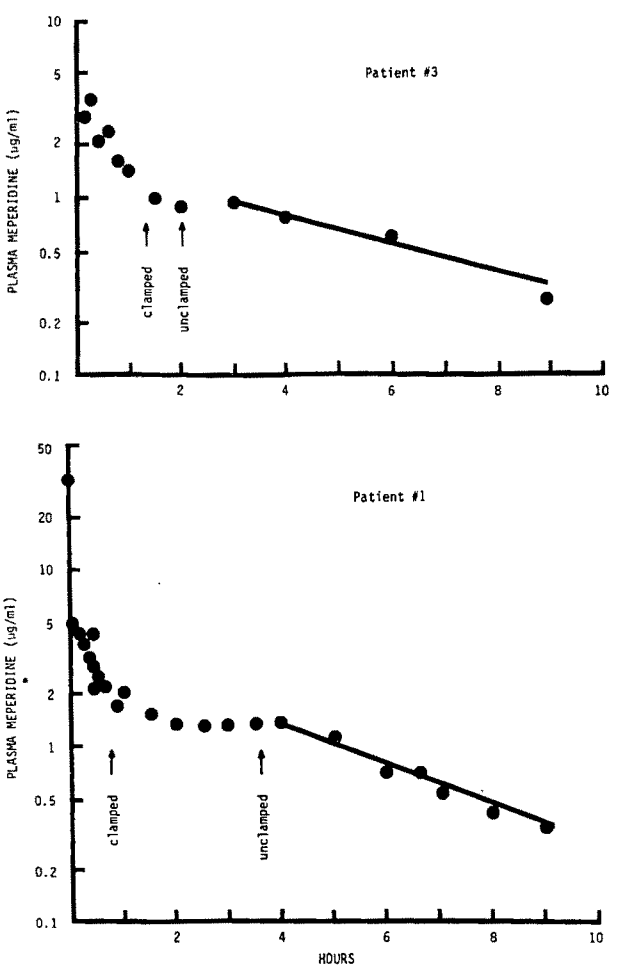


FIG 2. Semilogarithmic plots of plasma meperidine concentration (●) vs time for patients #1 and #3. Solid line through the terminal data points was calculated by linear regression of the natural logarithm of concentration against time and used for the determination of half-life. Times at which the arterial vessel was clamped and unclamped are indicated by arrows.

Finally, clearances and volumes of distribution were normalized to body weight.

Results

Semilogarithmic plots of plasma meperidine concentration vs time for two patients are shown in Fig 2. As can be seen, the curves appear to be biexponential except for some deviation during the time the arterial vessels were clamped during the surgical procedure. Once the clamps were removed, a log-linear decay resumed. These two plots are representative of the data for all six patients.

The model-independent pharmacokinetics calculated from the meperidine plasma concentration-time data are shown in Table 2. Half-life (t½) averaged 4.4 hours (range: 2.3 to 5.5), total plasma clearance (CL_T) 10.4 ml/min/kg (range: 5.5 to 13.5), and apparent volume of distribution (Vd_β) 3.7 L/kg (range: 2.5 to 6.1).

Discussion

Although meperidine is eliminated primarily by hepatic metabolism, our data indicate that the enzymatic systems responsible do not appear to be saturated by large doses. If the results of the present study are compared with those reported by Mather et al (5), who administered a total intravenous dose of 50 mg, and by Stambaugh et al (3), who gave 26 mg/m^2 intravenously (equal to 50 mg for an average surface area of 1.92 m^2) (Table 3), the agreement among the values for half-life, total plasma clearance, and apparent volume of distribution is very good. This is in spite of the fact that Stambaugh et al (3) studied normal volunteers and Mather et al (5) studied surgical patients undergoing orthopedic procedures when anesthetized with techniques different from

TABLE 2

Pharmacokinetic Data following Intravenous Injection of 5 mg/kg of Meperidine

Patient	t½	CL_T		Vd_β	
		L/min	ml/min/kg	L	L/kg
	hr				
1	2.34	1.03	13.5	210	2.76
2	5.50	1.07	12.9	509	6.13
3	3.15	0.349	6.34	158	2.87
4	5.22	1.11	12.2	306	3.36
5	5.14	0.446	5.50	203	2.51
6	5.22	0.793	12.2	313	4.82
Mean	4.43	0.800	10.4	283	3.74
±SD	1.33	0.332	3.54	126	1.43

TABLE 3

Comparison of Pharmacokinetics of Meperidine following High and Low Doses

Parameter	Present study	Mather et al (4)	Stambaugh et al (5)
Dose	5 mg/kg (≅375 mg)	50 mg	26 mg/m^2 (≅50 mg)
n	6	29	6
t½ (hr)	4.43 ± 1.34	3.1 ± 1.4	3.93 ± 0.33
CL_T			
L/min	0.80 ± 0.33		
ml/min/kg	10.4 ± 3.54	12.0 ± 5.0	
Vd_β (L)	283 ± 126	203 ± 99	242 ± 57

those employed in the present study. Comparison of the results of our study with either of the previous two studies using an unpaired *t*-test showed no significant differences in half-life, total plasma clearance, or apparent volume of distribution ($p < 0.025$). Therefore, the pharmacokinetics of meperidine following intravenous administration are apparently linear, at least at doses up to 5 mg/kg.

No metabolites were seen in any of the patient plasma samples. The sensitivity of the assay used in this study for normeperidine, the major active metabolite, is approximately 0.1 μg/ml. Plasma normeperidine levels are in the range of 0.25 to 0.5 μg/ml following cummulative doses of meperidine ranging from 900 to 7000 mg (6). Therefore, normeperidine levels would be expected to be below the sensitivity of this assay following single dose administration of 5 mg/kg, and thus were not detected in any of the plasma samples assayed in the present study.

The findings in the present study indicate that meperidine at doses as high as 5 mg/kg does not saturate the mechanisms responsible for elimination of the drug from the body. Similarly, the disposition of meperidine is not drastically affected by anesthetics or by the trauma of the surgical procedure itself. Changes in meperidine profiles that occurred during the clamping of the great vessels in our patients suggest that temporary occlusion of major arterial vessels is associated with alteration in the disposition of meperidine. Resumption of normal log-linear decay following removal of these clamps indicates, however, that these changes are only transitory.

Meperidine at the large doses used in the present study provides excellent analgesia with predictable disposition in surgical patients, but it should be used with extreme caution due to the possibility of an increase in side effects associated with large doses of narcotics.

REFERENCES

1. Asatoor AM, London DR, Milne MD, Siemenhoff ML. The excretion of pethidine and its derivatives. Br J Pharmacol 1963;20:285–298.
2. Klotz U, McHorse TS, Wilkinson GR, Schenker S. The effect of cirrhosis on the disposition and elimination of meperidine in man. Clin Pharmacol Ther 1974;16:667–675.
3. Stambaugh JE, Wainer IW, Sanstead JK, Hemphill DM. The clinical pharmacology of meperidine—comparison of routes of administration. J Clin Pharmacol 1976;16:245–256.
4. Burns JJ, Berger BL, Lief PA, Wollack A, Papper EM, Brodie BB. The physiological disposition and fate of meperidine (Demerol) in man and a method for its estimation in plasma. J Pharmacol Exp Ther 1974;16:667–675.
5. Mather LE, Tucker GT, Pflug AE, Lindop MJ, Wilkerson C. Meperidine kinetics in man. Clin Pharmacol Ther 1975;17:21–30.
6. Szeto HH, Inturrisi CE. Simultaneous determination of meperidine and normeperidine in biofluids. J Chromatogr 1976;125: 503–510.

ANESTH ANALG
60:12-17, 1981

Combination of Pancuronium and Metocurine: Neuromuscular and Hemodynamic Advantages over Pancuronium Alone

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LEBOWITZ, P. W., RAMSEY, F. M., SAVARESE, J J., ALI, H. H., AND DEBROS, F. M.: Combination of pancuronium and metocurine: neuromuscular and hemodynamic advantages over pancuronium alone. Anesth Analg 1981;60:12-17.

Combination of pancuronium and metocurine or pancuronium and *d*-tubocurarine produces potentiation of neuromuscular blocking effects such that administration of relatively small doses of these drugs can yield clinically effective neuromuscular blockade. The clinical characteristics of the block produced in A.S.A. class I-II patients during N_2O-narcotic-thiopental anesthesia by the pancuronium-metocurine combination at the calculated ED_{95} (N = 8) and at twice the ED_{95} (N = 9) were compared with the block produced by pancuronium alone at its ED_{95} (N = 20) and at twice the ED_{95} (N = 6). Onset time (from drug injection to 95% twitch suppression) and the maximum twitch depression achieved were comparable between corresponding groups, but the 25% recovery time (from drug injection to 25% recovery of twitch height) was significantly shorter in the groups that received the pancuronium-metocurine combination. Furthermore, at twice the ED_{95}, heart rate increased significantly more in the pancuronium group than in the pancuronium-metocurine combination group. Mean systemic blood pressure did not change significantly in either group. We conclude that patients given a combination of pancuronium and metocurine in large doses experience less hemodynamic change and more rapid recovery of neuromuscular function than do patients given equivalent doses of pancuronium alone.

Key Words: NEUROMUSCULAR RELAXANTS: pancuronium; NEUROMUSCULAR RELAXANTS: metocurine; INTERACTIONS (DRUG): neuromuscular relaxants; NEUROMUSCULAR RELAXANTS: hemodynamic effects.

WHEN USED in doses sufficient to provide ideal conditions for endotracheal intubation, all non-depolarizing neuromuscular blocking drugs in current anesthetic practice produce cardiovascular changes and have relatively long durations of action. Hence, the proper selection of a non-depolarizing neuromuscular blocking drug depends upon recognizing its autonomic and cardiovascular side effects and administering the dose appropriate to achieve the desired degree of muscle relaxation, speed of onset, and duration of block for a given clinical situation.

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Received from the Anesthesia Services, Massachusetts General Hospital and the Department of Anaesthesia, Harvard Medical School, Boston, Massachusetts. Accepted for publication October 4, 1980.

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It was recently demonstrated (1) that significant potentiation of neuromuscular blockade occurred when pancuronium and metocurine or pancuronium and *d*-tubocurarine were administered in combination. Either combination produced a similar depth of block at roughly half the doses predicted from adding neuromuscular blocking effects determined for any of these drugs given alone. We postulate that clinically employing such low drug doses might reduce their autonomic and cardiovascular side effects and might shorten their duration of action.

The present study was undertaken to determine whether the combination of pancuronium and metocurine during N_2O-narcotic-thiopental anesthesia does, in fact, offer any advantage over pancuronium alone, in terms of minimizing hemodynamic changes and shortening the duration of neuromuscular blockade.

Methods

Forty-three consenting A.S.A. class I-II patients of either sex undergoing elective surgical procedures

were studied. No patient had neuromuscular, renal, or hepatic disease, nor was any patient receiving medication known to affect myoneural transmission.

Patients were premedicated with diazepam, 0.15 mg/kg orally, and meperidine, 1 mg/kg IM, 1 hour before arrival in the operating room. Additional diazepam (to a total of 0.3 mg/kg) and meperidine (to a total of 3 mg/kg) were given intravenously before induction of anesthesia until the patient was well sedated. After thiopental, 3 mg/kg IV, for induction, anesthesia was maintained with 67% nitrous oxide in oxygen (4 L/2 L/min). Ventilation was assisted, when necessary, to approximate normocarbia. Stimulation of the ulnar nerve at the wrist was performed with 23-gauge steel needle electrodes that delivered square wave pulses 0.2 msec in duration at 0.15 Hz, repeated every 10 seconds. The stimuli were delivered at supramaximal voltage by a Grass S88 stimulator (Grass Instrument Co, Quincy, MA) through an SIU 5 isolation unit. Evoked force of thumb adduction was measured with a Grass FT 10 force-displacement transducer.

A 10-minute period without stimulation of any kind was utilized to obtain stable control measurements of systemic blood pressure (by arm sphygmomanometer), heart rate, and twitch height. Neuromuscular blockade was produced with one of four separate drug protocols, delivered as a single intravenous bolus. Group I (N = 20) received 0.07 mg/kg of pancuronium, the ED_{95} for neuromuscular blockade determined by Savarese et al (2). Group II (N = 8) was given the ED_{95} for the pancuronium-metocurine combination, calculated as 0.018 mg/kg of pancuronium plus 0.072 mg/kg of metocurine (1). Group III (N = 6) received approximately twice the ED_{95} for pancuronium, 0.15 mg/kg, and Group IV (N = 9) was given twice the ED_{95} for the pancuronium-metocurine combination, 0.036 mg/kg and 0.144 mg/kg, respectively.

Systemic blood pressure and heart rate were measured each minute in patients in Groups III and IV for the first 10 minutes after injection of the neuromuscular blocking drug(s). The trachea was then intubated and the conditions of jaw and laryngeal relaxation noted. Additional thiopental and meperidine were given subsequently as required for anesthesia, but no further neuromuscular blocking drugs were administered until twitch height had recovered spontaneously to greater than 25% of control. Residual neuromuscular blockade was antagonized at the conclusion of surgery using atropine, 0.02 mg/kg, and neostigmine, 0.05 mg/kg IV.

The conduct of the study of groups I and II patients differed only in that the trachea was intubated as soon as relaxation was deemed adequate and that hemodynamic measurements were only performed in a routine manner.

Onset time (time from drug injection to 95% depression of twitch height), maximum block achieved, 5% and 25% recovery times (time from drug injection to 5% and 25% recovery of twitch height, respectively), mean systemic blood pressure, and heart rate were measured. Means for group I were compared with those for group II, and group III was compared with group IV using Student's t-test. Differences were considered significant at $p < 0.05$.

Results

Bolus administration of the calculated ED_{95} for neuromuscular blockade for pancuronium (group I) yielded greater than 99% depression of twitch height with an onset time of 4.2 minutes (Fig 1); intubation conditions were assessed after this point as satisfactory, although cord movement was occasionally noted. Patients in group II (ED_{95} for pancuronium-metocurine combination) similarly achieved 99% depression of twitch height with an onset time of 5.1 minutes (Fig 2); intubating conditions were also essentially the same. Both 5% and 25% recovery times, however, were significantly ($p < 0.05$) shorter in patients receiving the pancuronium-metocurine combination than in patients given pancuronium alone (Table).

Parallel results were obtained when comparing neuromuscular blockade produced by higher doses of pancuronium (group III) and the pancuronium-me-

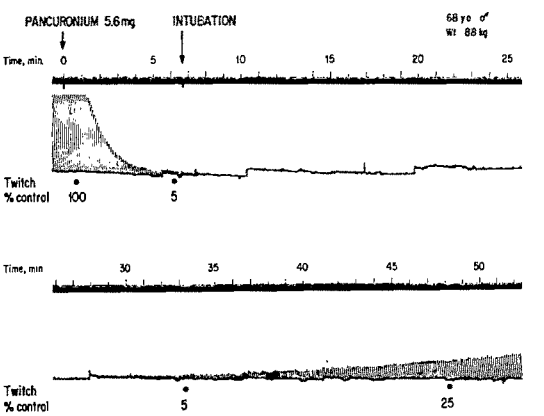


FIG 1. Representative recording of evoked thumb twitch with stimulation of the ulnar nerve at the wrist indicating neuromuscular blockade produced by a bolus injection of pancuronium, 0.07 mg/kg (ED_{95}). Onset of neuromuscular blockade (twitch 5% of control) occurs in 6 minutes; 25% recovery takes place 48 minutes after injection.

tocurine combination (group IV) (Figs 3 and 4). Again, onset time for pancuronium alone was somewhat, but not significantly, shorter than that for the drug combination (1.8 minutes vs 2.6 minutes), and the maximum block was similar in both groups (100% for pancuronium alone vs 99.4% for the drug combination). Likewise, recovery times were considerably shorter in patients receiving the pancuronium-metocurine combination when compared with times for patients given pancuronium alone. Whereas the difference in 5% recovery time was not statistically significant, the difference in 25% recovery time between group III and group IV was significant ($p < 0.02$) (Table).

Mean systemic blood pressure was not altered significantly from control in either group III or group IV; nor was there any significant difference in mean systemic blood pressure change when comparing group III with group IV (Fig 5). Notably, however, twice the ED_{95} for pancuronium caused heart rate to increase significantly ($p < 0.01$) from control. This increase in heart rate was apparent within 2 minutes (from a control of 76 beats/min to 90 beats/min) and

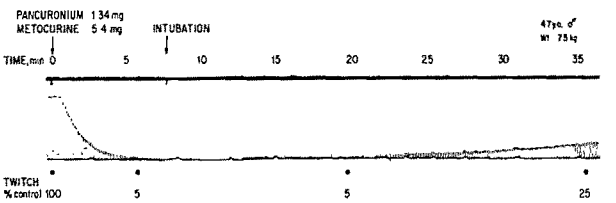


FIG 2. Representative recording of evoked thumb twitch depicting neuromuscular blockade produced by the combination of pancuronium, 0.018 mg/kg, and metocurine, 0.072 mg/kg (ED_{95} for this drug combination). Twitch is suppressed to 5% of control in 5 to 6 minutes following drug injection, proceeds to complete abolition by 9 to 10 minutes, and recovers spontaneously to 25% of control by 35 to 36 minutes following injection. This relatively slow onset of block and relatively rapid return of function typifies the clinical use of the pancuronium-metocurine combination in low doses.

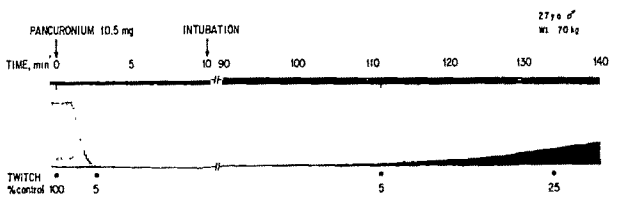


FIG 3. Representative recording of evoked thumb twitch illustrating the rapid production of neuromuscular blockade (100% twitch suppression) by pancuronium, 0.15 mg/kg, (twice the ED_{95}). Onset (twitch 5% of control) is seen within 2 to 3 minutes and 100% twitch suppression soon thereafter. Twitch does not return to 5% of control until 111 minutes after injection; 25% recovery is prolonged to 134 minutes.

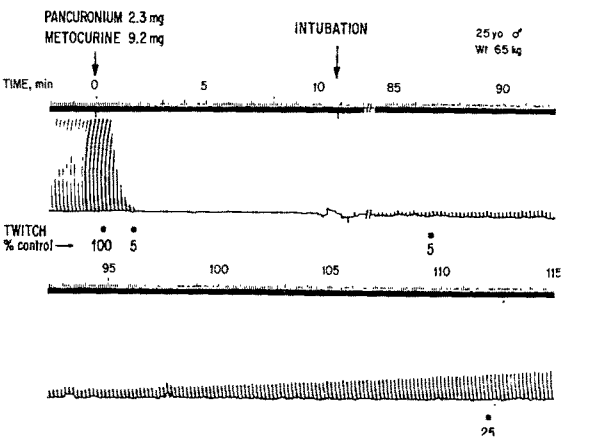


FIG 4. Representative recording of evoked thumb twitch showing twitch reduced to 5% of control within approximately 90 seconds after administration of twice the ED_{95} of the pancuronium-metocurine combination. Full twitch suppression occurs 2 minutes following injection, an exceptionally rapid response. Nonetheless, spontaneous recovery of neuromuscular function to 5% of control takes place in 86 to 87 minutes, and 25% recovery in 112 minutes. Rapid return of function may be anticipated with the pancuronium-metocurine combination in comparison with pancuronium alone, even at these relatively large doses.

TABLE

Neuromuscular Blockade and Recovery*

Group	N	Drug(s)	Dose	Onset of block	Maximum block achieved	Spontaneous recovery	
						5%	25%
			mg/kg	*min*	%	*min*	
I	20	Pancuronium	0.07	4.2 ± 0.5	99.2 ± 0.3	42.8 ± 2.5	63.6 ± 3.2
II	8	Pancuronium and metocurine	0.018 0.072	5.1 ± 1.3	99.0 ± 0.7	30.4 ± 5.2†	47.6 ± 4.4†
III	6	Pancuronium	0.15	1.8 ± 0.2	100	129 ± 10	159 ± 18
IV	9	Pancuronium and metocurine	0.036 0.144	2.6 ± 0.6	99.4 ± 0.4	88 ± 17	108 ± 9‡

* Values are means ± SEM.

† $p < 0.05$, compared to data for pancuronium alone.

‡ $p < 0.02$, compared to data for pancuronium alone.

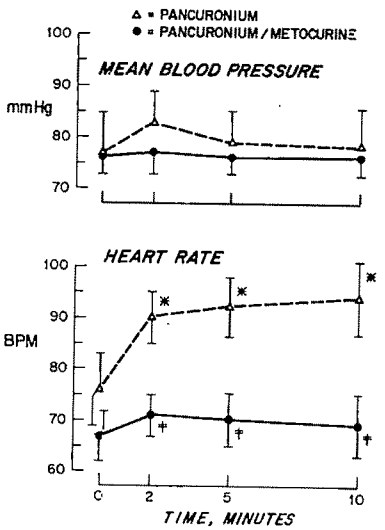


FIG 5. Hemodynamic response to bolus administration of pancuronium or the pancuronium-metocurine combination at twice the ED_{95} for neuromuscular blockade. With pancuronium, mean systemic blood pressure increases slightly but not significantly from control, whereas with the pancuronium-metocurine combination mean systemic blood pressure remains essentially unchanged; the difference between the two groups is not significant. Heart rate, on the other hand, increases significantly following pancuronium, both with regard to control ($p < 0.01$)* and in comparison to the pancuronium-metocurine combination ($p < 0.02$).‡ Following injection of the pancuronium-metocurine combination, heart rate remains essentially unchanged.

was sustained through the entire 10-minute measurement period (94 beats/min). Twice the ED_{95} of the pancuronium-metocurine combination, on the other hand, produced essentially no alteration in heart rate at 2, 5, or 10 minutes. The differences in heart rate change between group III and group IV were highly significant ($p < 0.02$) at all points of measurement.

Discussion

Currently available non-depolarizing neuromuscular blocking drugs all cause alteration in cardiovascular performance when used in clinically effective doses (3). Furthermore, such cardiovascular changes are largely dose-dependent (2, 4). As demonstrated by autonomic dose-response curves in cats (5, 6) and supported by cardiovascular studies in man, *d*-tubocurarine (4, 7) and metocurine (2, 8) both cause greater ganglionic blockade (and blood pressure reduction) at high dose ranges, while large doses of pancuronium (7, 9, 10) and gallamine (11, 12) are associated with vagal blockade (and heart rate acceleration). Additional mechanisms, notably histamine release in the cases of *d*-tubocurarine (13) and metocurine (2), and augmented catecholamine effects in the cases of pancuronium (14, 15) and gallamine (16), unquestionably contribute to the observed changes.

Because these side effects are largely dose related, autonomic and cardiovascular alterations should be minimized if clinically effective neuromuscular blockade can be produced by giving relatively small drug doses. Potentiation of neuromuscular blockade by combinations of pancuronium and metocurine or pancuronium and *d*-tubocurarine provides the setting for testing this hypothesis.

At the lower of two doses that were tested, the combination of pancuronium and metocurine was as effective as pancuronium alone in producing satisfactory intubating conditions and surgical relaxation. Because such low doses of the combination (as compared to pancuronium alone) were used, redistribution kinetics might have resulted in earlier reduction in the level of each neuromuscular blocking drug at its pre- or postsynaptic site of action (1, 17–21) and, consequently, earlier restoration of normal neuromuscular transmission. Apart from speculation about mechanism, the pancuronium-metocurine combination is clearly associated with more rapid spontaneous recovery of neuromuscular function than is pancuronium alone following similar degrees of neuromuscular blockade.

As expected, the duration of neuromuscular blockade was prolonged, and the onset time shortened by increasing the dose of drug administered from ED_{95} to twice the ED_{95}. However, the relative lengthening of duration was significantly less for the pancuronium-metocurine combination than for pancuronium alone. Presumably, the mechanism is the same as that described above.

Even when used at twice the ED_{95}, the pancuronium-metocurine combination maintained cardiovascular function in a remarkably stable fashion. Both mean systemic blood pressure and heart rate remained within 6% of control throughout the entire 10-minute study period. Twice the ED_{95} of pancuronium, on the other hand, significantly increased heart rate (>20% above control), although mean systemic blood pressure was not elevated beyond 8% of control.

From a practical viewpoint, several conclusions may be drawn. First, continued study of pancuronium and metocurine in combination supports our earlier contention that neuromuscular blockade is potentiated by their administration in combination. Second, spontaneous recovery of neuromuscular function from equivalent degrees of neuromuscular blockade occurs more rapidly with the pancuronium-metocurine combination than with pancuronium alone. The earlier the return of neuromuscular function, the easier it is for antagonism of residual neuromuscular blockade

to be accomplished by administration of anticholinesterase agents. Every patient studied had full restoration to control twitch height and clinically adequate recovery of muscle strength when atropine, 0.02 mg/kg, and neostigmine, 0.05 mg/kg, were given after 25% recovery of twitch height.

Third, the time from bolus injection of the nondepolarizer drug(s) studied to achievement of 95% twitch height depression is longer, even at twice the ED_{95}, than that for succinylcholine, 1 mg/kg (63 ± 4.3 seconds) to attain complete abolition of thumb twitch (22). In comparison, the use of large doses (0.15 to 0.20 mg/kg) of pancuronium to expedite endotracheal intubation during rapid induction of anesthesia has been reported by Brown et al (23) as a practical alternative to succinylcholine in patients in whom succinylcholine is contradicted, e.g., burns, massive trauma, and denervation injury. Brown et al noted onset time (to 90% twitch suppression) to be only 1.25 minutes. Although twice the ED_{95} of the pancuronium-metocurine combination gave satisfactory intubating conditions (95% twitch suppression) in 2.6 ± 0.6 minutes, we found that twice the ED_{95} of pancuronium alone was more consistent than the combination in producing rapid onset (1.8 ± 0.2 minutes). In comparing these differences, it is worthy of note that the 25% recovery time following this dose of pancuronium is more than 2½ hours, as opposed to 1¾ hours for the combination. This point may have some bearing, particularly in short operative procedures when extubation is desired at the conclusion of surgery.

Fourth, the use of a large dose of pancuronium as part of a thiopental-nitrous oxide-meperidine relaxant technique inevitably results in a significant increase in heart rate with a modest (8%) elevation of mean systemic blood pressure. In contrast, the pancuronium-metocurine combination, even at twice the ED_{95}, maintains heart rate and mean systemic blood pressure very close to control levels. The hemodynamic stability conferred upon the patient by the pancuronium-metocurine combination offers advantages to patients with coronary artery disease, aortic stenosis, and mitral stenosis, in which an increased heart rate may prove deleterious to cardiac performance. Brown et al (23), using fentanyl instead of meperidine, did not observe a significant tachycardia with high dose pancuronium; this finding requires further investigation.

In summary, the combination of pancuronium and metocurine offers several advantages over the use of pancuronium alone. Nevertheless, monitoring of neuromuscular function is advised when using the metocurine-pancuronium combination, both to assess the depth of neuromuscular blockade and to evaluate recovery from it.

REFERENCES

1. Lebowitz PW, Ramsey FM, Savarese JJ, Ali HH. Potentiation of neuromuscular blockade in man produced by combinations of pancuronium and metocurine or pancuronium and *d*-tubocurarine. Anesth Analg 1980;59:604–609.
2. Savarese JJ, Ali HH, Antonio RP. The clinical pharmacology of metocurine: dimethyltubocurarine revisited. Anesthesiology 1977;47:277–284.
3. Lebowtiz PW, Savarese JJ. Clinical and autonomic effects of neuromuscular blockers. In: Hershey SG, ed. Refresher courses for anesthesiology, vol 8. American Society of Anesthesiologists. Philadelphia: JB Lippincott, 1980:103–14.
4. Munger WL, Miller RD, Stevens WC. The dependence of *d*-tubocurarine-induced hypotension on alveolar concentration of halothane, dose of *d*-tubocurarine, and nitrous oxide. Anesthesiology 1974;40:442–448.
5. Hughes R, Chapple DJ. Effects of non-depolarizing neuromuscular blocking agents on peripheral autonomic mechanisms in cats. Br J Anaesth 1976;48:59–67.
6. Savarese JJ. The autonomic margins of safety of metocurine and *d*-tubocurarine in the cat. Anesthesiology 1979;50:40–46.
7. Stoelting RK. The hemodynamic effects of pancuronium and *d*-tubocurarine in anesthetized patients. Anesthesiology 1972;36:612–615.
8. Stoelting RK. Hemodynamic effects of dimethyltubocurarine during nitrous oxide-halothane anesthesia. Anesth Analg 1974;53:513–515.
9. Kelman GR, Kennedy BR. Cardiovascular effects of pancuronium in man. Br J Anaesth 1971;43:335–338.
10. Loh L. The cardiovascular effects of pancuronium bromide. Anaesthesia 1970;25:356–363.
11. Stoelting RK. Hemodynamic effects of gallamine during halothane-nitrous oxide anesthesia. Anesthesiology 1973;39:645–647.
12. Eisele JH, Marta JA, Davis HS. Quantitative aspects of the chronotropic and neuromuscular effects of gallamine in anesthetized man. Anesthesiology 1971;35:630–633.
13. Moss J, Rosow CE, Savarese JJ, Philbin D, Howland L. Hypotensive action of *d*-tubocurarine in man: histamine predominance. Anesthesiology 1980;53:(suppl 3) S-279.
14. Segarra Domenech J, Carlos Garcia R, Rodriquez Sasiain JM, et al. Pancuronium bromide: an indirect sympathomimetic agent. Br J Anaesth 1976;48:1143–1148.
15. Docherty JR, McGrath JC. Sympathomimetic effects of pancuronium bromide on the cardiovascular system of the pithed rat: a comparison with the effects of drugs blocking the neuronal uptake of noradrenaline. Br J Pharmacol 1978;64:589–599.
16. Brown BR, Crout JR. The sympathomimetic effect of gallamine on the heart. J Pharmacol Exp Ther 1970;172:266–273.
17. Riker WF. Pre-junctional effects of neuromuscular blocking and facilitatory drugs. In: Katz RL, ed. Muscle relaxants. New York: American Elsevier, 1975:59–102.
18. Standaert FG. The action of *d*-tubocurarine on the motor nerve terminal. J Pharmacol Exp Ther 1964;143:181–186.
19. Bowman WC, Webb SN. Tetanic fade during partial transmission failure produced by non-depolarizing neuromuscular blocking drugs in the cat. Clin Exp Pharmacol Physiol 1976;3:545–555.
20. Galindo A. The role of pre-junctional effects in myoneural transmission. Anesthesiology 1972;36:598–608.

21. Su PC, Su WL, Rosen AD. Pre- and post-synaptic effects of pancuronium at the neuromuscular junction of the mouse. Anesthesiology 1979;50:199–204.
22. Cullen DJ. The effect of pretreatment with nondepolarizing muscle relaxants on the neuromuscular blocking action of succinylcholine. Anesthesiology 1971;35:572–578.
23. Brown EM, Krishnaprasad D, Smiler BG. Pancuronium for rapid induction technique for tracheal intubation. Can Anaesth Soc J 1979;26:489–491.

Use of PEEP in Management of the Postoperative Bleeding Heart

This prospective study included 406 consecutive adults who had heart surgery with extracorporeal circulation. Fifteen patients (3.7%) bled at the rate of 200 ml/hr or more in the postoperative period. Of the 15 patients who bled 13 had undergone coronary artery operation. After all clotting factors and, when applicable, hypertension had been checked and corrected, positive end-expiratory pressure (PEEP) was used in managing the bleeding of these patients. Before institution of PEEP, the average blood loss was 330 ml/hr for 1 to 5 hours. After PEEP was instituted in the 11 patients in whom bleeding was controlled, an average output of 25 ml/hr for 1 to 10 hours was recorded. Patients were kept on PEEP for 5 to 10 hours. In seven patients hemorrhage was controlled with 10 cm H_2O of PEEP; four patients required 15 cm of PEEP to stop bleeding; three were explored for continuous bleeding on 15 cm of PEEP; and one was explored because of hypotension on 15 cm of PEEP. In 11 of the 15 patients who bled after surgery (73%), operation was avoided by judicious use of PEEP. The authors believe that PEEP increases mediastinal pressure and that the overdistended lung can obliterate some bleeding in the mediastinum, thus controlling bleeding in many of these patients. *(Ilabaca PA, Ochsner JL, Mills NL: Positive end-expiratory pressure in the management of the patient with a postoperative bleeding heart. Ann Thorac Surg 1980;30:281–284)*

Vascular and Uterine Responses to Dobutamine and Dopamine

Dopamine, a naturally occurring catecholamine precursor of norepinephrine, has been used in the treatment of cardiogenic shock. Following intravenous administration it increases cardiac output, blood pressure, and renal blood flow. Dobutamine is a directly acting inotropic agent which increases myocardial contractility without significantly changing blood pressure. This study was devised to compare the effects of these two drugs on uterine blood flow (UBF), uterine tonus (UT), mean arterial blood pressure (MAP), and heart rate (HR). Chronically instrumented pregnant ewes near term were infused with different concentrations of dopamine and dobutamine while HR, MAP, UT, and UBF were recorded continuously. Dopamine produced a decrease in UBF and an increase in MAP and UT while the HR response was variable. Dobutamine administration resulted in a marked increase in HR and a decrease in UBF, while MAP and UT remained essentially unchanged. Uterine vascular resistance increased with both drugs during high-dosage administration, but the rise was most pronounced following dopamine infusion. Since dobutamine exhibits less alpha-adrenergic activity than dopamine this drug would seem to be preferred when an inotropic agent is required for treatment of the pregnant patient. *(Fishburne JI, Meis PJ, Urban RB, et al: Vascular and uterine responses to dobutamine and dopamine in the gravid ewe. Am J Obstet Gynecol 1980;137:944–952)*

ANESTH ANALG
60:18-20, 1981

Temperature and Potency of *d*-Tubocurarine and Pancuronium in Vitro

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FARRELL, L., DEMPSEY, M. J., WAUD, B. E., AND WAUD, D. R.: Temperature and potency of *d*-tubocurarine and pancuronium in vitro. Anesth Analg 1981;60:18-20.

The concentrations of *d*-tubocurarine and pancuronium producing 50% block of the indirectly elicited twitch were determined in isolated mouse nerve-diaphragm preparations at 37 and 25 C. The contralateral side was used as a control in a 2 × 2 factorial analysis of variance. Cooling shifted the dose-response curves for both drugs to the left, but only slightly (from 1.69 ± 0.022 μM to 1.49 ± 0.021 μM with *d*-tubocurarine and from 0.65 ± 0.012 μM to 0.46 ± 0.009 μM with pancuronium). The dose-response relationship was, however, so steep (Hill coefficient approximately 5 to 6) that a slight horizontal shift of the dose-response curve corresponds to a considerable decrease in the twitch response at a concentration midway between the curves. Thus, studies using only the concentration that produces partial block of twitch responses misleadingly suggest a large effect of temperature. Similarly, if in another system the curve were to shift to the right even only slightly, a temperature effect in the reverse direction might be reported. It is concluded that temperature appears to have little influence on cellular potency of neuromuscular blocking agents.

Key Words: NEUROMUSCULAR RELAXANTS: *d*-tubocurarine; NEUROMUSCULAR RELAXANTS: pancuronium; TEMPERATURE: neuromuscular relaxants.

THE EFFECT of temperature on the cellular action of neuromuscular blocking agents remains unclear. Indeed, only one study has presented a full dose-response curve (1). Some papers report competitive blocking agents to be more potent at 37 C than at 24 C (2-4), whereas others report the reverse (5-8). One study agreed with both of these findings (9). We, therefore, undertook a quantitative analysis of the effect of temperature on *d*-tubocurarine and pancuronium under well controlled conditions in vitro.

Methods

The experiments were done on isolated mouse phrenic nerve-hemidiaphragm preparations in Krebs' solution (Na^+, 138 mM; K^+, 5.9 mM; Ca^{2+}, 2.5 mM; Mg^{2+}, 1.22 mM; C^-, 123 mM; $H_2PO_4^-$, 1.2 mM, HCO_3^-, 25 mM; glucose, 115 mM) bubbled with 95%/5% oxygen/carbon dioxide. The nerve was stimulated every 10 seconds with pulses of 0.3-msec duration and twice maximal intensity, and the resulting twitch response was recorded isometrically. After approximately 30 minutes for equilibration, either *d*-tubocurarine or pancuronium was added to the bath in increasing concentrations. The resulting steady-state twitch responses were used as dose-response data for estimation of the ED_{50} of the blocking agent, i.e., the concentration reducing the twitch response to one half. Specifically, the observed values were fitted with a logistic function of the form twitch height (as fraction of control level) = $1 - \text{concentration}^P/(\text{concentration}^P + K^P)$. This function yields a sigmoidally decreasing curve of slope governed by P (P is equivalent to a Hill coefficient (10)) and an ED_{50} equal to K. The curve was fitted by a nonlinear iterative least squares technique analogous to that used previously in this laboratory (11), and yielding estimates of P and K along with standard errors of these estimates. This basic experimental design was expanded into a 2 × 2 factorial design in which temperature (37 C vs 25 C) and side (left vs right) were the two factors. The resulting analysis of variance could then be used to test for parallelism of curves and to estimate the effects of choice of side as well as of temperature. The first of these two factors provides both a convenient

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Supported by National Institute of Neurological and Communicative Disorders and Stroke Grant NS 12255.
Received from the Departments of Pharmacology and Anaesthesia, University of Massachussetts Medical School, Worcester, Massachussetts. Accepted for publication October 6, 1980.
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control and a built-in measure of how great random variation should be.

Results

Both *d*-tubocurarine and pancuronium produced concentration-dependent reductions in twitch height (Figs 1 to 4). The dose-response curves are quite steep with P in the range 5 to 6 (vs 1 for most dose-response curves (12)). In all figures the two dose-response relationships had similar slopes so the data were fitted with curves with a common slope. In both series of experiments the neuromuscular blocking agents were more potent at the lower temperature (Figs 1 and 2). The effect was slight but significant. The effect of choice of side was negligible (Figs 3 and 4). The Table summarizes the statistical estimates.

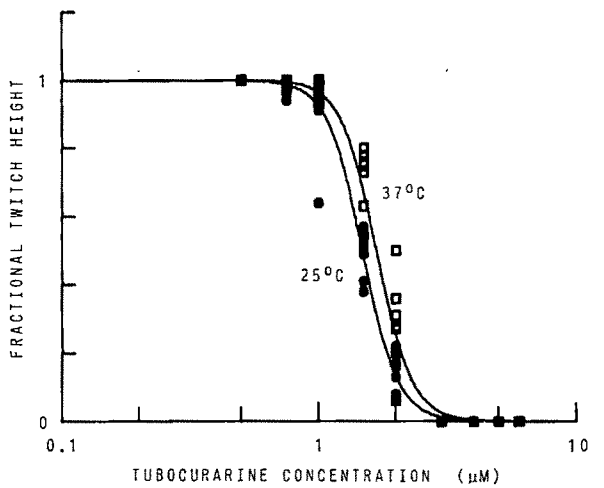


FIG 1. Effect of temperature on response of isolated mouse phrenic nerve-diaphragm preparations to *d*-tubocurarine. Ordinates, twitch heights as a fraction of control level before blocking agent was added; abscissae, concentrations of tubocurarine; squares, responses at 37 C; circles, response at 25 C. Curves are fitted by least squares (see text).

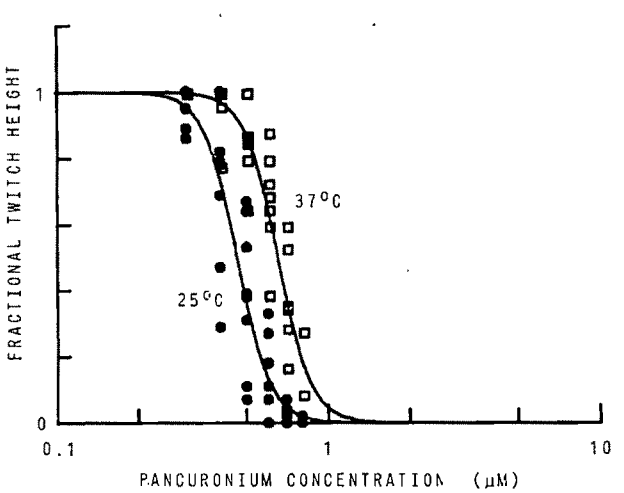


FIG 2. Effect of temperature on neuromuscular block produced by pancuronium. Plot as in Fig 1.

Discussion

The experiments show a slight, but statistically demonstrable effect of temperature. The use of the diaphragm with its bilateral symmetry provides a convenient null effect for comparison. Comparison of Figs 1 and 2 with Figs 3 and 4 shows that even though the temperature effect is "statistically significant" the magnitude of the effect is, for all practical purposes, negligible.

It is interesting to view previous reports in the light of the present observations. As already mentioned, temperature effects in opposite directions have been

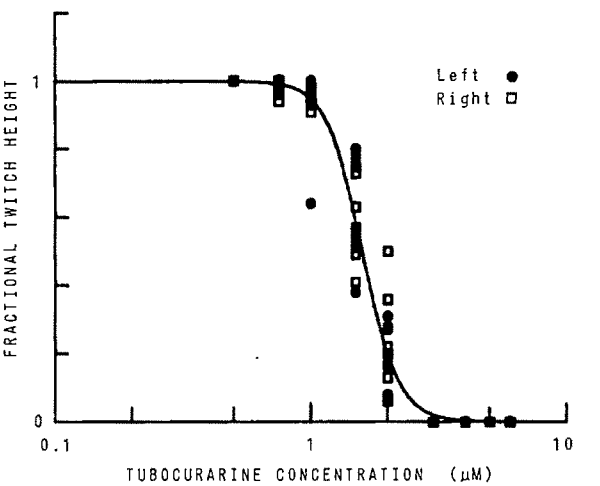


FIG 3. Effect of choice of side on response to tubocurarine. Plot as in Fig 1 except that squares are observations from right hemidiaphragm, circles from left.

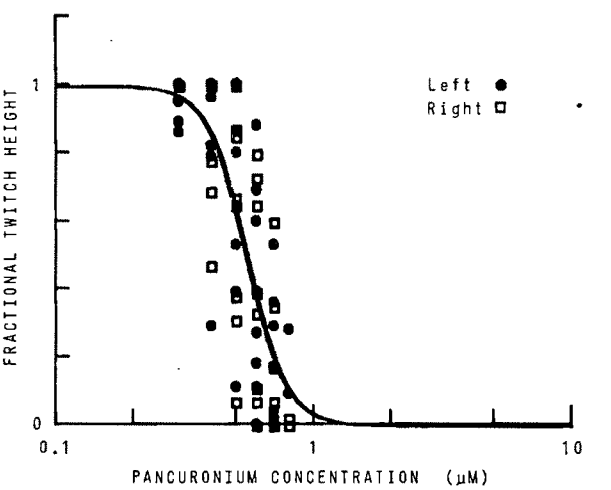


FIG 4. Effect of side on response to pancuronium. Plot as in Fig 3.

TABLE

ED_{50} Values (means ± SE)

	25 C	37 C	Left	Right
			μM	
Tubocurarine	1.49 ± 0.021	1.69 ± 0.022	1.60 ± 0.027	1.59 ± 0.027
Pancuronium	0.46 ± 0.009	0.65 ± 0.012	0.56 ± 0.020	0.54 ± 0.020

reported in different studies, as well as in the same one. Careful examination of results such as those in Figs 1 or 2 suggests a possible explanation. Because of the steepness of the curves they need only to be separated slightly to generate a situation in which a twitch response might be only slightly blocked at 37 C, yet markedly blocked when the temperature was lowered to 25 C. For example, in Fig 2, use of 0.5 μM pancuronium would give little block at 37 C and a rather intense one at 25 C. Such a change in twitch height might be interpreted as meaning temperature "greatly" (2) affects the action of the drug. However, when the full dose-response curve is viewed, and in particular when the horizontal shift of the curve is examined, the temperature effect is far less impressive.

There is no reason to expect that our observed shift of the dose-response curve to the left with lower temperature would carry over to other muscles, or species, or both. In fact, Holmes et al (1), in a similar preparation, but from a muscle in a different species, have already found a change in the reverse direction. However, given the steepness of the dose-response relationship involved, it is important with a shift in either direction to look not at the extent to which a particular twitch response is depressed, but rather at the shift of the whole dose-response curve, i.e., at the magnitude by which the anesthesiologist would have to change the dose that is to be administered. Unfortunately, most reports give only the former sort of observation. However, it is possible to estimate the extent of a horizontal shift if a value for the Hill coefficient is assumed. When this number is taken to be approximately 5 (as found here), effects of temperature turn out to be slight, not more than a factor of 2 in either direction. This is a small effect compared to patient-to-patient variation (13). Note that the present studies, done in vitro, allow one to examine the cellular action unperturbed by pharmacokinetic effects. In a patient the latter influence would be present and aggravate the uncertainty of a priori prediction of dosage requirement. Thus, taken all together, studies on the effect of temperature show no strong effect and, in turn, the anesthesiologist would not appear to gain any precision by trying to estimate temperature effects a priori. The preceding is not to imply that the anesthesiologist may not see a change in depth of block with a change in temperature in any given patient, but rather that prediction of the extent and direction will not be very reliable. As is generally the case with neuromuscular blocking agents, careful monitoring and direct titration of the drug against the patient, regardless of the latter's temperature, will be the most reliable way to optimize dosage.

REFERENCES

1. Holmes PEB, Jenden DJ, Taylor DB: The analysis of the mode of action of curare on neuromuscular transmission; the effect of temperature changes. J Pharmacol Exp Ther 1951;103:382–402.
2. Bigland B, Goetzee B, Maclagen J, Zaimis E: The effect of lowered muscle temperature on the action of neuromuscular blocking drugs. J Physiol 1958;144:425–434.
3. Canard TH, Zaimis E: The effect of lowered muscle temperature on the action of neuromuscular blocking drugs in man. J Physiol 1959;149:112–119.
4. Ham J, Miller RD, Benet LZ, Matteo RS, Roderick LL: Pharmacokinetics and pharmacodynamics of *d*-tubocurarine during hypothermia in the cat. Anesthesiology 1978;49:324–329.
5. McKleeven JR, Sokoll MD, Gergis SD, Dretchen KL: Absence of recurarization upon rewarming. Anesthesiology 1973;38: 153–156.
6. Miller RD, Van Nyhuis LS, Eger EI: The effect of temperature on a *d*-tubocurarine neuromuscular blockade and its antagonism by neostigmine. J Pharmacol Exp Ther 1975;195:237–241.
7. Miller RD, Roderick LL: Pancuronium-induced neuromuscular blockade, and its antagonism by neostigmine at 29, 37, and 41C. Anesthesiology 1977;46:333–335.
8. Miller RD, Agoston S, van der Pol F, Booij LHD, Crul JF, Ham J: Hypothermia and pharmacokinetics and pharmacodynamics of pancuronium in the cat. J Pharmacol Exp Ther 1978;207: 532–538.
9. Foldes FF, Kuze S, Offenberg T: The influence of temperature on the activity of neuromuscular blocking agents. Fed Proc 1975;34:752.
10. Brown WEL, Hill AV: The oxygen-dissociation curve of blood, and its thermodynamical basis. Proc R Soc Lond [Biol] 1923;94: 297–334.
11. Waud DR: Analysis of dose-response curves. In: Daniel EE, Paton DM, eds. Methods in pharmacology: vol 3, smooth muscle. New York: Plenum, 1975;471–506.
12. Clark AJ: Mode of action of drugs on cells. London: Arnold, 1933.
13. Katz RL: Neuromuscular effects of *d*-tubocurarine, edrophonium and neostigmine in man. Anesthesiology 1967;28:327–336.

ANESTH ANALG
60:21-27, 1981

Effects of Fentanyl on Adrenergic Function in Canine Coronary Arteries

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RORIE, D. K., MULDOON, S. M., AND TYCE, G. M.: Effects of fentanyl on adrenergic function in canine coronary arteries. Anesth Analg 1981;60:21-27.

The effects of fentanyl on sympathetic nerve endings in canine coronary arteries have been examined. Measurements were made of changes in endogenous norepinephrine in isolated coronary artery in the presence of fentanyl, and of the effects of fentanyl on norepinephrine release and metabolism using superfused strips of coronary arteries in which transmitter stores had been prelabeled with [^{3}H]norepinephrine. [^{3}H]Norepinephrine and its ^{3}H metabolites were separated from samples of superfusate (physiologic salt solution flowing continuously over the prelabeled coronary artery) by column chromatography and measured by scintillation spectrometry. The addition of fentanyl (2×10^{-6} and 8×10^{-6} M) caused the overflow of total radicactivity (radiolabeled norepinephrine and radiolabeled metabolites of norepinephrine entering the superfusate) to increase significantly above basal levels in both unstimulated and electrically stimulated arteries. The increased overflow could be accounted for by a small increase in norepinephrine and a sizeable increase in 3,4-dihydroxyphenylglycol, the metabolite arising from the intraneuronal metabolism of norepinephrine. Because this metabolite is without agonist activity and the increases in norepinephrine were small, fentanyl in the concentrations studied had minimal effects on adrenergic neurotransmission in this vascular bed.

Key Words: ANALGESICS: fentanyl; HEART: coronary arteries; SYMPATHETIC NERVOUS SYSTEM: norepinephrine.

THE NARCOTIC fentanyl has been used extensively for several years as a part of neuroleptanesthesia in doses between 5 and 20 μg/kg. At this dose it has been found to have minimal adverse cardiovascular effects (1-5). Recently anesthesiologists have advocated the use of fentanyl in much higher doses (50 to 100 μg/kg) as the anesthetic agent for patients undergoing cardiovascular surgery (6-8). Available information indicates that fentanyl is a good choice in that it is associated with minimal disturbance of cardiovascular function (7, 8). It is unknown, however, whether fentanyl produces changes in the release, disposition, or metabolism of norepinephrine (NE) at neuroeffector junctions in the coronary circulation. Such information is important in view of recent evidence suggesting that in certain circumstances sympathetic alpha-receptor-mediated coronary vasoconstriction can reduce the coronary vasodilation caused by local metabolic mechanisms (9, 10). The sympathetic nervous system thus appears to "fine tune" the coronary blood flow control mechanism.

We have studied the in vitro effects of fentanyl on the coronary artery of the dog using two methods: (a) By measuring changes in endogenous NE in coronary artery in the presence of fentanyl; and (b) by examination of the effects of fentanyl on NE release and metabolism using strips of coronary artery in which transmitter stores had been prelabeled with [^{3}H]NE. This yields valuable information on metabolites of NE that are important markers for the study of changes in NE release and disposition.

Methods

Preparation and Superfusion of Vascular Preparations

Experiments were performed on helical strips of canine coronary artery. The dogs (20 to 30 kg) were anesthetized with pentobarbital (50 mg/kg IV), the chest was opened and the heart removed. The anterior interventricular branch of the left coronary artery and the right coronary artery were dissected from their

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Supported in part by National Institutes of Health grants HL-23217, GM-25926, and NS-9143, a grant from the American Society of Anesthesiologists, and by the Parker B. Francis Foundation.
Received from the Departments of Anesthesiology and Physiology, Mayo Clinic, Rochester, Minnesota. Accepted for publication October 7, 1980.
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point of origin distally to a diameter of 1 mm, cleaned of perivascular tissue, and cut into helical strips. A total of 24 dogs were studied.

In 15 experiments, arterial strips were incubated for 2 hours in Krebs-Ringer's solution (11) containing 6.7×10^{-7} M L-[7-^{3}H]NE (specific activity 3.8 Ci/mmole; New England Nuclear, Boston, MA), disodium ethylenediaminetetraacetate (EDTA) (0.1 mg/ml), and ascorbic acid (0.2 mg/ml). The strips were mounted for superfusion in a cylindrical superfusion chamber maintained continuously at 37 C. To remove extraneuronal and extravesicular [^{3}H]NE from the tissues, the strips were superfused for 90 minutes and the superfusate was then discarded.

For electrical stimulation (ES) of adrenergic nerves, two platinum wires (0.5 mm in diameter) were placed parallel to, and in contact with, the strips; both the strips and electrodes were superfused continuously at 3 ml/min with Krebs-Ringer's solution aerated with 95% O_2 and 5% CO_2. Electrical stimulation consisted of rectangular impulses (10 V, 2 msec duration, 2 Hz). Impulses were supramaximal as was confirmed by comparing fractional release of [^{3}H]NE (calculated as described by Graefe et al (12)) from coronary artery, in the presence of cocaine (10^{-5} M) and corticosterone (4×10^{-5} M), using two stimulation voltages. NE released with stimulation for 2 minutes at 10 V, 2 msec, 2 Hz was found to be 96% of that released with stimulation at 9 V, 2 msec, 2 Hz (n = 2).

In two experiments tetrodotoxin (final concentration 10^{-6} M) was added to the superfusate.

In 18 experiments endogenous NE was extracted and measured in control arteries and in arteries after incubation for 45 minutes in Krebs-Ringer's solution containing fentanyl (2×10^{-6} or 8×10^{-6} M). The incubation fluid was aerated continuously with 95% O_2 and 5% CO_2.

To determine whether 3,4-dihydroxyphenylglycol (DOPEG) formed in the tissue was further metabolized, three arterial strips were incubated for 2 hours in Krebs-Ringer's solution containing [^{14}C]DOPEG (specific activity 47 mCi/mmole; Research Products International Corp, Elk Grove Village, IL) at concentration of 2.1×10^{-6} M, 2.1×10^{-7} M, or 2.1×10^{-8} M. After incubation, the tissues and media were analyzed for content of [^{3}H]DOPEG and metabolites.

Basal Efflux of [^{3}H]NE and Its Metabolites: Effects of Fentanyl

In these experiments, strips of coronary artery after incubation in [^{3}H]NE were superfused, and the superfusate was collected continuously in 18-ml samples (6-minute intervals). After the first sample was collected, fentanyl (2×10^{-6} M or 8×10^{-6} M) was added to the superfusion fluid and an additional three 18-ml samples of superfusate were collected. The fentanyl was then removed from the superfusion fluid and four additional samples of superfusate were collected. Three samples (basal, during fentanyl and basal, and postfentanyl) were analyzed by column chromatography for [^{3}H]NE and radiolabeled metabolites of NE. After collection of the last sample of superfusate, the artery was used for extraction of NE and metabolites.

Efflux of [^{3}H]NE and Its Metabolites during Electrical Stimulation: Effects of Fentanyl

After the 90-minute washout, an 18-ml sample of superfusate was collected under basal conditions. Electrical stimulation (2 Hz) of the strip was then started and continued for 42 minutes, during which time seven successive 18-ml samples of superfusate were collected. After discontinuing stimulation, four more samples of superfusate were collected before the experiment was terminated. In other preparations, fentanyl (2×10^{-6} or 8×10^{-6} M) was added to the superfusion fluid during electrical stimulation (12th through the 30th minute of the experiment, during the second, third, and fourth periods of stimulation). Five representative samples of superfusate were collected for determination of [^{3}H]NE and the radiolabeled metabolites of NE. These were: (a) basal (0 to 6 minutes); (*b*) during stimulation, but before fentanyl (6 to 12 minutes); (*c*) during stimulation and fentanyl (12 to 30 minutes); (*d*) during stimulation 30 to 42 minutes after fentanyl administration was completed; and (e) during basal after fentanyl treatment and 42 to 60 minutes after stimulation had been discontinued. At the end of each experiment, the tissue was used for extraction of [^{3}H]NE and its metabolites.

Isolation and Measurement of Endogenous NE from Arterial Tissue and Incubation Fluid

Endogenous NE was extracted from strips of coronary artery by immersing them for two 30-minute periods in separate 5-ml aliquots of 1 N acetic acid containing 0.03 mM EDTA and 0.2 mg/ml ascorbic acid (13). NE was isolated from the extracts of artery and from incubation fluid by absorption chromatography on alumina and cation-exchange resin Amberlite CG50 (Rohm and Haas, Co, Philadelphia, PA) as described previously (14). The concentration of NE in

25 μl of this extract was determined by high pressure liquid chromatography with electrochemical detection. Separation was done by using a μBondapak C_{18} column (Waters Associates, Inc, Milford, MA) and a mobile phase of 0.07 M NaH_2PO_4, 0.2 mM EDTA, 2 mM heptanesulfonate, and 6% methanol at pH 4.8. The electrochemical detector was set at 0.7 V against a silver/silver chloride reference electrode. The average recovery of 10 ng of NE added to extracts of arteries was 70.6 ± 6.0% (mean ± SEM) n = 5.

Separation of [^{3}H]NE and Radiolabeled Metabolites

[^{3}H]NE was separated from its metabolites in the superfusates and in the extracts of artery prepared after termination of superfusion, by the method of Graefe et al (15). Carrier substances, 0.1 mg each of NE, normetanephrine (NMN), 3,4-dihydroxymandelic acid (DOMA), DOPEG, 3-methoxy-4-hydroxymandelic acid, 3-methoxy-4-hydroxyphenylglycol; 3.0 mg of sodium metabisulfite; and 0.6 ml of 2 N HCl were added to each sample of superfusate and to each extract of artery.

After incubation of tissues in [^{14}C]DOPEG, metabolites in tissues and in the incubation fluid were separated by the method used for separation of [^{3}H]-NE and its metabolites. Because interferences were observed previously between the DOPEG and DOMA metabolite fraction (16), all DOPEG, DOMA, and NE data were corrected for cross-contamination.

Radioactivity Measurements

Aliquots (1 ml) of superfusate and of the effluents, and eluates from columns were added to 10 ml of Insta-Gel (Packard Instrument Co, Inc, Downers Grove, IL), and the radioactivity was measured in a liquid scintillation counter. Corrections for quenching were made with an external standard. The counting efficiency was 35%. Most of the samples were counted for 10 minutes or long enough to reach 10,000 counts.

Calculations

Fractional rate of loss of radioactivity from the artery during each time period was calculated by dividing the radioactivity in each superfusate by that present in the tissue. The amount of tritium in the tissue at any given time was calculated by adding to the radioactivity in the artery at the end of the study all the tritium collected in samples of superfusate from that time to the end of sample collection.

Analysis of Data

Results are expressed as means ± SEM. For statistical evaluation of data, Student's *t*-test was used; *p* values <0.05 were considered significant. Because of slight variations in tissue weights, all values have been expressed on the basis of an artery weight of 100 mg.

Results

Effect of Fentanyl on Basal Efflux of [^{3}H]NE and Its Metabolites from Coronary Arteries

Addition of fentanyl (final concentrations 2×10^{-6} and 8×10^{-6} M) to the fluid, superfusing a strip of coronary artery prelabeled with [^{3}H]NE, caused the overflow of total radioactivity (all of the radioactivity leaving the neuroeffector junctions in the artery that is washed away by the Krebs-Ringer's solution; included are [^{3}H]NE as well as the ^{3}H metabolites of NE produced through neuronal and extraneuronal metabolism of NE) to increase significantly above basal levels (Fig 1) although the tension did not change.

The major impact of fentanyl in increasing the overflow of radioactivity was to cause an increase in the [^{3}H]DOPEG and [^{3}H]OMDA [o-methylated, deaminated metabolites, (3-methoxy-4-hydroxymandelic acid and 3-methoxy-4-hydroxyphenylglycol)] in the superfusate (Table 1). The [^{3}H]DOPEG fraction was increased significantly above basal levels when either concentration of fentanyl was present in the superfusate, and decreased significantly when fentanyl was removed from the superfusion fluid. At the higher fentanyl concentration, [^{3}H]OMDA was also increased significantly above basal. Analysis of arterial tissue after study showed no differences in the content of NE or metabolites of NE between arteries treated with the high and low concentrations of fentanyl.

DOPEG is a metabolite of NE that diffuses across membranes rather easily (17) and the possibility was considered that the OMDA that was formed under basal conditions was produced from DOPEG. After incubation of coronary arteries in [^{14}C]DOPEG at 2.1×10^{-6} M or at 2.1×10^{-7} M, there was significant uptake (defined as [^{14}C]DOPEG in the artery plus ^{14}C-labeled metabolites in the artery or in the fluid); this uptake accounted for 7.5% and 7.8%, respectively, of the total DOPEG in the bath. After incubation in 2.1×10^{-8} M DOPEG, the amounts of radiolabeled DOPEG in tissue, or of metabolites in tissue or in fluid, were not significant when corrected for interference between fractions (16). Only trivial amounts of radio-

labeled OMDA were formed from either 2.1×10^{-6} M or 2.1×10^{-7} M DOPEG (Table 2). Significant amounts of DOMA were, however, formed at both concentrations.

Effect of Fentanyl on Efflux of [^{3}H]NE and Its Metabolites from Coronary Artery during Electrical Stimulation

Electrical stimulation predictably increased the percent of loss of total radioactivity from the tissue (Fig 2). This release was abolished in two experiments by the addition of tetrodotoxin at a concentration (10^{-6} M), which has been shown to abolish the increase in sodium conductance associated with propagated nerve impulse (18). When fentanyl was added to the superfusate at a concentration of 8×10^{-6} M, the loss of total ^{3}H from the tissue was significantly enhanced, but 2×10^{-6} M fentanyl was without effect.

The amounts of [^{3}H]NE in superfusate were also increased by stimulation (Fig 2), but the increased release of [^{3}H]NE was not sustained (Fig 3). More [^{3}H]NE was present in superfusate when 8×10^{-6} M fentanyl was added during stimulation, but the decrease with time still occurred. The addition of 2×10^{-6} M fentanyl during stimulation was without effect on NE overflow.

Electrical stimulation increased the amounts of all metabolites of [^{3}H]NE overflowing into superfusate (Table 3). The addition of 8×10^{-6} M fentanyl during stimulation caused an increase in [^{3}H]DOPEG in the superfusate; this increase was not significantly different from that caused by the addition of fentanyl under basal conditions (30.94 ± 5.99 compared to 53.53 ±

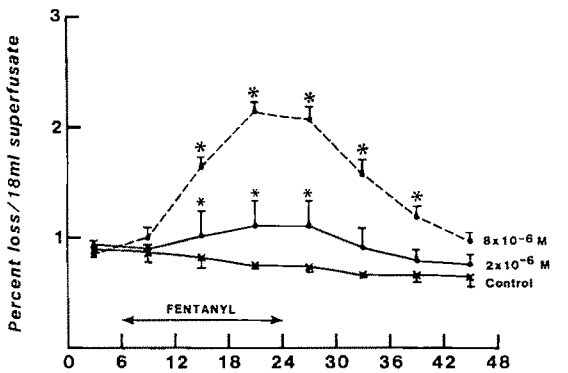


FIG 1. Fractional loss of total radioactivity with time from unstimulated strips of dog coronary artery prelabeled with [^{3}H]NE. Superfusate was collected in 6-minute samples. Treatment: (×——×) control strips (superfusion with Krebs-Ringer's solution); (●——●) 2×10^{-6} M fentanyl, and (●- - -●) 8×10^{-6} M fentanyl between 6th and 24th minute. Values are means (± SEM); n = 5; * = $p < 0.05$ for differences from control strips.

TABLE 2

Uptake and Metabolism of DOPEG by Coronary Arteries*

Concentration of DOPEG†	Total uptake‡	DOPEG in tissue	DOMA in tissue and fluid	OMDA in tissue and fluid
2.1×10^{-6} M (3)	810 ± 28	278 ± 12	492 ± 24	45 ± 23
2.1×10^{-7} M (3)	83 ± 7	33 ± 5	42 ± 15	10 ± 6

* Data are shown as mean picomoles ± SEM. Abbreviations are defined in footnote to Table 1.

† Segments of coronary artery were incubated in Krebs-Ringer's solution containing [^{14}C]DOPEG for 2 hours. Total volume of the incubation bath was 5 ml. Number of determinations is shown in parentheses.

‡ Total uptake is shown as total ^{14}C in tissue plus ^{14}C-labeled metabolites in the incubation fluid.

TABLE 1

Effect of Fentanyl on Basal Release of [^{3}H]NE and Radiolabeled Metabolites of NE from Dog Coronary Arteries*

Parameter	NE	DOPEG	DOMA	NMN	OMDA
Radioactivity in superfusate†					
Basal‡	0.91 ± 0.68	26.51 ± 2.80	2.71 ± 0.60	0.31 ± 0.05	4.03 ± 0.65
Δ with fentanyl§					
2×10^{-6} M	0.48 ± 0.80	11.68 ± 4.04‖	0.22 ± 0.91	−0.01 ± 0.07	−0.07 ± 0.65
8×10^{-6} M	0.03 ± 0.33	53.53 ± 10.71‖	−0.91 ± 1.34	0.19 ± 0.10	3.21 ± 1.01‖
Residual tissue radioactivity¶					
No fentanyl	4237 ± 215	24 ± 0.64	93 ± 37	114 ± 13	188 ± 56
2×10^{-6} M fentanyl	2924 ± 612	31 ± 10	124 ± 59	69 ± 17	40 ± 10
8×10^{-6} M fentanyl	3385 ± 540	41 ± 74	119 ± 23	84 ± 16	90 ± 22

* Data are expressed per 100 mg of tissue to correct for small variations in the weights of the arteries; values are means ± SEM; n = 5. Abbreviations used are: NE, norepinephrine; DOPEG, 3,4-dihydroxyphenylglycol; DOMA, 3,4-dihydroxymandelic acid; NMN, normetanephrine; and OMDA, *o*-methylated, deaminated metabolites (3-methoxy-4-hydroxymandelic acid and 3-methoxy-4-hydroxyphenylglycol.

† 10^3 disintegrations per minute per 18 ml of superfusate.

‡ Geometric mean of values in periods 1 and 8 (before fentanyl and 18 to 24 minutes after removing fentanyl).

§ Geometric mean of values in periods 1 and 8 have been subtracted from those in period 4 when fentanyl was present.

‖ $p = <0.05$.

¶ Radioactivity remaining in the tissue at the end of the study.

10.74, Tables 1 and 3). The amounts of other metabolites in superfusate were not changed by fentanyl addition at 8×10^{-6} M. The addition of 2×10^{-6} M fentanyl during stimulation did not affect the amounts of [^{3}H]NE or its metabolites in superfusate (Table 3). No differences were found in the content of [^{3}H]NE or its metabolites in control or fentanyl-treated tissues at the end of the experiments (Table 3).

The tension generated in response to electrical stimulation of the arteries was not altered significantly by fentanyl. Stimulation (2 Hz) resulted in 0.15 ± 0.06 g tension in control arterial strips, 0.17 ± 0.06 g in strips treated with 2×10^{-6} M fentanyl, and 0.06 ± 0.06 g in strips treated with 8×10^{-6} M fentanyl.

Effect of Fentanyl on Endogenous NE Content

Because of the high fractional release of total radioactivity from coronary arteries in the presence of 8×10^{-6} M fentanyl (Fig 2), the possibility was consid-

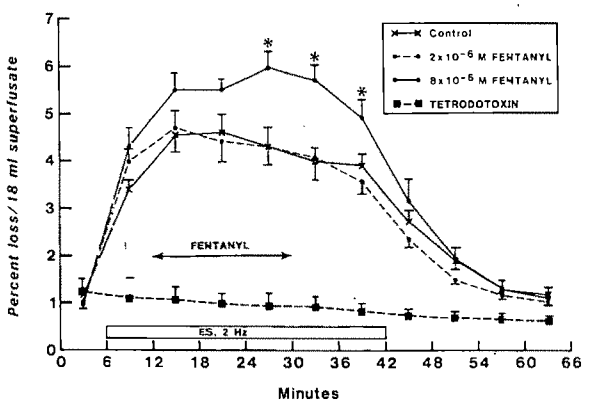


FIG 2. Fractional loss of total radioactivity with time from strips of dog coronary artery prelabeled with [^{3}H]NE and stimulated electrically at 2 Hz between the 6th and 42nd minute. Superfusate was collected in 6-minute samples. Treatment: (×——×), control strips (superfusion with Krebs-Ringer's solution); (■- - -■), 3×10^{-7} M tetrodotoxin present throughout superfusion; (●- - -●) 2×10^{-6} M fentanyl, and (●——●) 8×10^{-6} M fentanyl were present between 12th and 30th minute. Values are means (± SEM); n = 5; * = $p < 0.05$ for differences from control strips.

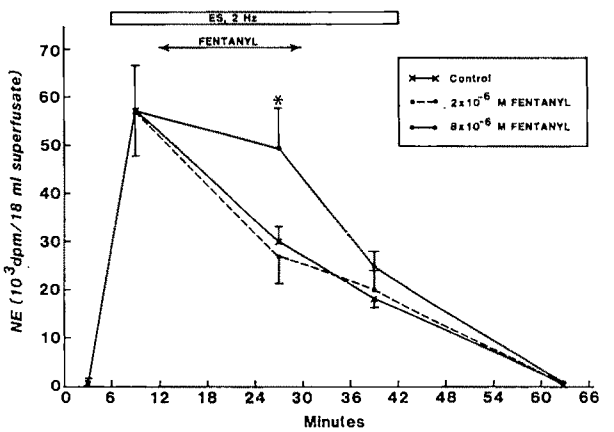


FIG 3. [^{3}H]NE in superfusate from prelabeled strips of dog coronary artery. [^{3}H]NE was separated from the other radiolabeled metabolites in selected superfusate samples by column chromatography. Electrical stimulation was applied between 6th and 42nd minute. Treatment: (×——×), control strips; (●- - -●), 2×10^{-6} M; and (●——●) 8×10^{-6} M fentanyl were present between 12th and 30th minute. Values are means (± SEM); n = 5; * = $p < 0.05$ for differences from control strips.

TABLE 3

Effect of Fentanyl on the Overflow of [^{3}H]NE and Radiolabeled Metabolites of NE during Electrical Stimulation (ES) (2 Hz) of Dog Coronary Artery*

Parameter	NE	DOPEG	DOMA	NMN	OMDA
Radioactivity in superfusate†					
Basal‡	0.62 ± 0.10	23.30 ± 1.90	3.12 ± 0.34	0.34 ± 0.03	4.72 ± 0.58
Δ with ES§	32.07 ± 4.67‖	32.01 ± 2.44‖	5.78 ± 1.08‖	2.85 ± 0.21‖	12.32 ± 0.73‖
Δ with fentanyl during ES¶					
2×10^{-6} M	−3.00 ± 3.37	23.03 ± 13.21	−1.01 ± 1.64	−0.15 ± 0.61	2.33 ± 3.44
8×10^{-6} M	16.74 ± 8.33#	30.94 ± 5.99#	0.45 ± 3.96	1.06 ± 0.72	3.35 ± 3.69
Residual tissue radioactivity**					
No fentanyl	2708 ± 435	45 ± 9	133 ± 10	63 ± 3	74 ± 23
2×10^{-6} M fentanyl	2918 ± 541	35 ± 4	113 ± 24	60 ± 9	55 ± 9
8×10^{-6} M fentanyl	2371 ± 236	30 ± 3	113 ± 9	55 ± 4	51 ± 7

* Data are expressed per 100 mg of tissue to correct from small variations in the weights of the arteries.Values are means ± SEM; n = 5. Abbreviations used are defined in footnote to Table 1.

† Data as 10^3 dpm per 18 ml of superfusate.

‡ Pooled geometric mean of prestimulation sample and sample collected 18 to 24 minutes after ES.

§ Calculated by subtracting basal release from the geometric mean of the values of the first and last periods of ES.

‖ p = <0.01.

¶ Change due to fentanyl was calculated by subtracting geometric mean of values obtained during ES before and after fentanyl.

p = <0.05.

** Radioactivity remaining in tissue (10^3 disintegrations per minute/100 mg) at end of the study.

ered that this compound might cause depletion of NE stores within the arteries. However, it was found that the endogenous NE content in arteries incubated for 45 minutes in Krebs-Ringer's solution without fentanyl was 0.39 ± 0.03 μg/g (mean ± SEM, n = 4) and with fentanyl (2×10^{-6} or 8×10^{-6} M) was 0.31 ± 0.04 μg/g and 0.36 ± 0.03 μg/g (n = 9), respectively. These were not significantly different from each other or from the NE content in control arteries or arteries without prior incubation (0.45 μg/g ± 0.05).

Discussion

The aim of the present study was to investigate the effect of fentanyl on NE release and disposition in the dog coronary artery. [^{3}H]NE labeling of the NE stores in the blood vessel was used because the amount of endogenous NE released from small strips of coronary arteries by nerve activity is difficult to quantitate biochemically. With the method, the interventricular branch of the left coronary artery and the right coronary artery were preincubated in [^{3}H]NE and then suspended in a superfusion apparatus. This system allows continuous collection of released [^{3}H]NE and the metabolites of NE, and in addition allows continuous recording of mechanical activity.

Results of the present study indicate that fentanyl increased the overflow of total radioactivity from both unstimulated and electrically stimulated canine coronary arteries. The increased overflow could be accounted for by a small increase in [^{3}H]NE and a sizeable increase in [^{3}H]DOPEG, the metabolite of NE shown in this and other tissues (11, 16, 19), to arise from the intraneuronal metabolism of NE. Since this metabolite is inactive physiologically (20) and the increases in unmetabolized [^{3}H]NE were modest, fentanyl, in the concentration studied, had minimal effects on adrenergic neurotransmission in this vascular bed.

At the low concentration of NE likely to be present in the synaptic cleft during unstimulated conditions, it is probable that NE is mainly removed by uptake into sympathetic nerves, yet OMDA, which arises from the postsynaptic metabolism of NE, increased when fentanyl was added to the superfusate. This therefore suggests that some degree of neuronal uptake blockade was produced by fentanyl. Fentanyl-induced neuronal blockade of NE uptake has been reported previously to occur in rabbit heart (21).

The concentrations of fentanyl used in this study approximate those calculated to be achieved in circulating blood (10^{-7} M) when fentanyl is given in the clinically used dose of 0.05 mg/kg of body weight. Although fentanyl had minimal effect on the overall release, disposition, or metabolism of the neurotransmitter in this vascular bed, analysis of the superfusate for ^{3}H metabolites of NE indicates that even in these relatively small doses fentanyl caused an impairment of the vesicular storage of NE, and also had an effect on neuronal re-uptake of NE, one of the mechanisms for removal of NE from the synaptic cleft. The combined effects of impaired storage of NE in intraneuronal storage vesicles and blockade of neuronal uptake should, theoretically, be manifested as increased amounts of [^{3}H]NE in this neuroeffector junction and increased amounts of [^{3}H]NE entering the superfusate. Small amounts of [^{3}H]NE increased the overflow, suggesting that the other mechanism for removing NE from the neuroeffector junction, extraneuronal uptake, was effective in removing NE from the cleft in this tissue, even in the low concentrations present at this time. The increase observed in the NE metabolite OMDA, considered to be extraneuronal in origin in this (19) and in other tissues (11, 16), supports this conclusion. Our data show that it was unlikely that the increases in OMDA were the results of further metabolism of DOPEG.

In unstimulated arteries, the fentanyl-induced increased formation of DOPEG suggests that fentanyl entered sympathetic nerve endings and caused release of NE from the vesicles. It was postulated that the increased cytoplasmic levels of NE might interfere with synthesis of NE by inhibiting tyrosine hydroxylase. However, prolonged incubation of arteries in Krebs-Ringer's solution containing fentanyl did not alter significantly the NE content of these tissues.

The NE content per unit weight in the coronary arteries was rather low (0.31 ± 0.04 μg/g) compared to other adrenergically innervated blood vessels which have ranged from 3.0 to 5.7 μg/g (14, 22). Further, the coronary artery appears to have release characteristics different from some other segments of the peripheral vasculature that have been studied (11). This is evident by the high fractional release of its neurotransmitter—up to 4% to 6% of its content every 6 minutes of electrical stimulation. The elimination of this release with tetrodotoxin, which blocks the nerve action potential, indicates that the release is neuronal in origin.

Further, the rapid decrease in [^{3}H]NE overflow into superfusate during continuous electrical stimulation at low frequencies (Fig 3) is far more precipitous than the drop observed in many other vessels (11, 23, 24). It is of interest that overflow of total radioactivity did

not parallel this decrease in [^{3}H]NE (Figs 2 and 3). Despite the increase in [^{3}H]NE and total ^{3}H overflow observed during electrical stimulation in control strips and in strips treated with fentanyl, little contractile response was observed and no significant difference in contractile response to electrical stimulation was observed between control and fentanyl-treated groups. This is in keeping with in vivo studies showing that the direct infusion of small amounts of NE into the coronary circulation causes only a transient coronary vasoconstriction followed by vasodilation, or only vasodilation (25–27). Thus the amount of NE shown to be released by fentanyl in these studies may not significantly alter coronary blood flow. Systemic hypertension, however, might be expected if fentanyl increased the amount of NE released from peripheral vasculature and this NE reached the systemic circulation. Only a few cases of fentanyl-induced systemic hypertension have been reported (28), even when fentanyl was used in high doses; this may be because most released NE was converted to DOPEG intraneuronally before its entering the neuroeffector junction, and because this NE metabolite does not have agonist properties. In addition, fentanyl in higher doses has been shown to cause blockade of postsynaptic alpha receptors (29), and this action would reduce the likelihood of hypertension.

REFERENCES

1. Holderness MC, Chase PE, Dripps RD. Use of a narcotic analgesic and a butyrophenone with nitrous oxide for general anesthesia. Anesthesiology 1963;24:336–40.
2. Gardocki JF, Yelnosky J. A study of some of the pharmacologic actions of fentanyl citrate. Toxicol Appl Pharmacol 1964;6:37–47.
3. Tammisto T, Takki S, Toikka P. A comparison of the circulatory effects in man of the analgesics fentanyl, pentazocine and pethidine. Br J Anaesth 1970;42:317–24.
4. Ostheimer GW, Shanahan EA, Guyton RA, Daggett WM, Lowenstein E. Effects of fentanyl and droperidol on canine left ventricular performance. Anesthesiology 1975;42:288–91.
5. Stoelting RK, Gibbs PS, Creasser CW, Peterson C. Hemodynamic and ventilatory responses to fentanyl-droperidol, and nitrous oxide in patients with acquired valvular heart disease. Anesthesiology 1975;42:319–24.
6. Stanley TH, Webster LR. Anesthetic requirements and cardiovascular effects of fentanyl-oxygen and fentanyl-diazepam-oxygen anesthesia in man. Anesth Analg 1978;57:411–16.
7. Stanley TH, Philbin DM, Coggins CH. Fentanyl-oxygen anesthesia for coronary artery surgery: cardiovascular and antidiuretic hormone responses. Can Anaesth Soc J 1979;26:168–72.
8. Lunn JK, Stanley TH, Eisele J, Webster L, Woodward A. High dose fentanyl anesthesia for coronary artery surgery: plasma fentanyl concentrations and influence of nitrous oxide on cardiovascular responses. Anesth Analg 1979;294:390–95.
9. Mohrman DE, Feigl EO. Competition between sympathetic vasoconstriction and metabolic vasodilation in the canine coronary circulation. Circ Res 1978;42:79–86.
10. Murray PA, Vatner SF. α-Adrenoceptor attenuation of the coronary vascular response to severe exercise in the conscious dog. Circ Res 1979;45:654–60.
11. Rorie DK, Muldoon SM, Tyce GM. Disposition of norepinephrine during nerve stimulation in dog saphenous vein. Am J Physiol 1980;239:H238–46.
12. Graefe KH, Stefano FJE, Langer SZ. Stereoselectivity in the metabolism of ^{3}H-noradrenaline during uptake into and efflux from the isolated rat vas deferans. Naunyn Schmiedebergs Arch Pharmacol 1971;270:210–14.
13. Levin JA. Paper chromatography assay of [^{3}H]norepinephrine and its five major metabolites. Anal Biochem 1973;51:42–60.
14. Muldoon SM, Tyce GM, Moyer TP, Rorie DK. Measurement of endogenous norepinephrine overflow from canine saphenous veins. Am J Physiol 1979;236:H263–67.
15. Graefe KH, Stefano FJE, Langer SZ. Preferential metabolism of (−)-^{3}H-norepinephrine through the deaminated glycol in rat vas deferens. Biochem Pharmacol 1973;22:1147–60.
16. Muldoon SM, Vanhoutte PM, Tyce GM. Norepinephrine metabolism in canine saphenous vein: prevalence of glycol metabolites. Am J Physiol 1978;234:H235–43.
17. Fiebig ER, Trendelenburg U. The neuronal and extraneuronal uptake and metabolism of ^{3}H-(−)-noradrenaline in the perfused rat heart. Naunyn Schmiedebergs Arch Pharmacol 1978;303:21–35.
18. Narahashi T. Chemicals as tools in the study of excitable membranes. Physiol Rev 1974;54:813–89.
19. Rorie DK, Shepherd JT. Norepinephrine content release and disposition in isolated dog coronary artery. Proc Soc Exp Biol Med (in press, 1980).
20. Langer SZ, Rubio MC. Effects of the noradrenaline metabolites on the adrenergic receptors. Naunyn Schmiedebergs Arch Pharmacol 1973;276:71–88.
21. Montel H, Starke K. Effects of narcotic analgesics and their antagonists on the rabbit isolated heart and its adrenergic nerves. Br J Pharmacol 1973;49:628–41.
22. Vanhoutte PM, Coen EP, DeRidder WJ, Verbeuren TJ. Evoked release of endogenous norepinephrine in the canine saphenous vein; inhibition by acetylcholine. Circ Res 1979;45:608–14.
23. Endo T, Starke K, Bangerter A, Taube HB. Presynaptic receptor systems on the noradrenergic neurones of the rabbit pulmonary artery. Naunyn Schmiedebergs Arch Pharmacol 1977;296:229–47.
24. Cubeddu L, Barnes EM, Langer SZ, Weiner N. Release of norepinephrine and dopamine-B-hydroxylase by nerve stimulation. I. Role of neuronal and extraneuronal uptake and of alpha presynaptic receptors. J Pharmacol Exp Ther 1974;190:431–50.
25. Ross G. Adrenergic responses of the coronary vessels. Circ Res 1976;39:461–65.
26. Gaal PG, Kattus AA, Kolin A, Ross G. Effects of adrenaline and noradrenaline on coronary blood flow before and after beta-adrenergic blockade. Br J Pharmacol 1966;26:713–22.
27. Berne RM. Effect of epinephrine and norepinephrine on coronary circulation. Circ Res 1958;6:644–55.
28. Dubois-Primo, J. Comparison between fentanyl and morphine for use in analgesic anesthesia during open heart surgery. Acta Anaesthesiol Belg 1975;26:5–24.
29. Toda N, Hatano Y. Alpha-adrenergic blocking action of fentanyl on the isolated aorta of the rabbit. Anesthesiology 1977;46:411–16.

ANESTH ANALG
60:28-32, 1981

Lidocaine Aerosols Do Not Prevent Allergic Bronchoconstriction

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DOWNES, H., AND HIRSHMAN, C. A.: Lidocaine aerosols do not prevent allergic bronchoconstriction. Anesth Analg 1981; 60:28-32.

To test the effectiveness of local anesthetic aerosols in asthma, we compared the protection afforded by lidocaine and saline aerosols to bronchoconstriction provoked by inhalation of *Ascaris* antigen aerosols in five previously sensitized, anesthetized Basenji-Greyhound, crossbred dogs. Pulmonary resistance (R_L) was determined by the method of Von Neergaard and Wirz, and blood lidocaine levels were determined by gas chromatography. Lidocaine, 4%, was administered as an aerosol for 10 minutes before challenge with *Ascaris* antigen and again during the 10-minute challenge with *Ascaris* antigen. Lidocaine aerosols frequently elicited a slight increase in R_L before antigen challenge, whereas saline aerosols did not alter R_L. Despite a large dose (approximately 10 mg/kg), which produced blood levels of 0.6 to 3.3 μg/ml, lidocaine afforded no protection against antigen challenge: R_L increased from a control mean of 4.2 ± 1.7 (SEM) cm H_2O/liters/sec to 26.9 ± 9.3 after challenge in lidocaine-treated dogs, and from 2.9 ± 0.6 to 22.8 ± 5.1 in saline-treated dogs. In contrast, lidocaine aerosols prevented the 7-fold increase in R_L elicited by challenge with citric acid aerosols, demonstrating an adequate block of irritant reflexes. The failure of lidocaine aerosols to protect against antigen-induced bronchoconstriction indicates that the concentrations achieved in lung by this route are inadequate to relax smooth muscle directly.

Key Words: ANESTHETICS, local; LUNG: bronchi.

LOCAL ANESTHETICS, administered systemically (1-3) or as aerosols (4, 5), have been used to block a variety of airway reflexes in man, and may be useful in treating or preventing bronchoconstriction during anesthesia (6). Bronchoconstriction can be triggered by different types of stimuli. These may provoke irritant reflexes, release allergic mediators from airway mast cells, or directly constrict bronchial smooth muscle. We have previously shown that lidocaine, administered by intravenous infusion, was far more effective at preventing irritant than at preventing allergic bronchoconstriction in a dog model of reactive airway disease (7). Lidocaine, at higher concentrations than can be produced safely in blood, is known to relax bronchial smooth muscle directly (8, 9) and to impair mediator release (10). Since the aerosol route increases the concentration gradient from lung to blood, lidocaine presumably might be a more effective bronchodilator by this route. Therefore, the purpose of our study was to determine whether administration of lidocaine by the aerosol route could prevent antigen-induced bronchoconstriction.

Methods

Five Basenji-Greyhound, crossbred dogs, three naturally allergic and two previously sensitized to *Ascaris* antigen, were selected for use in these experiments on the basis of a large and consistent increase in pulmonary resistance (R_L), and decrease in dynamic compliance (C_{dyn}) during repeated challenges with *Ascaris* antigen aerosols. The dogs, each weighing approximately 20 kg, were not premedicated and were anesthetized standing, supported by a sling. After induction of anesthesia with thiamylal, 12 mg/kg IV, the dogs were paralyzed with succinylcholine, 1 mg/kg, intubated with an 8.5- to 9.0-mm endotracheal tube, and manually ventilated with 100% oxygen. Additional increments of thiamylal, 2 mg/kg, and succinylcholine, 0.2 mg/kg, were administered as needed

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Supported by National Institution of Health grants GM 24524 and HL-25831, and the Department of Anesthesiology Research and Education Society.
Received from the Departments of Pharmacology and Anesthesiology, School of Medicine, University of Oregon Health Sciences Center, Portland, Oregon. Accepted for publication September 16, 1980.
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at approximately 20-minute intervals. An esophageal balloon (Dynasciences, Blue Bell, PA) was placed in the esophagus under direct vision and positioned at the point where recorded end-expiratory pressure was lowest. The balloon contained 0.8 ml of air. A separate catheter, connected to suction, was placed in the esophagus to keep it empty of air and liquid.

For measurement of R_L and C_{dyn}, the dogs were ventilated for approximately 30 seconds with a piston-type ventilator (Harvard Apparatus Co, Inc, Millis, MA) set to deliver a tidal volume of 400 ml at a frequency of 15/min. Transpulmonary pressure was measured with a differential pressure transducer (Model 270 Hewlett-Packard, Waltham, MA) connected to the esophageal balloon and to a needle inserted into the endotracheal tube. Airflow ($\dot{V}$) was measured with a calibrated pneumotachograph head (Hewlett-Packard 2100) and a differential flow transducer (Hewlett-Packard 47304A). Pressure and flow signals were recorded with a Hewlett-Packard 47601 recorder.

C_{dyn} was calculated by dividing tidal volume by the difference in pressure between points of zero flow. Resistance was calculated using the method of Von Neergaard and Wirz (11), by dividing transpulmonary pressure minus elastic pressure (as determined from C_{dyn}), by $\dot{V}$ at mid-tidal volume. Apparatus resistance, determined by ventilating a mechanical lung analog with known parameters, was subtracted from the resulting value to give R_L. All volumes were corrected to BTPS. R_L and C_{dyn} were calculated from a mean of seven consecutive breaths. End-tidal CO_2 concentration was monitored with a Beckman LB-1 infrared analyzer (Beckman Instruments, Inc, Palo Alto, CA) and maintained at 4.5%.

Aerosols were delivered by a Hudson 3000 nebulizer (Hudson Co, Temecula, CA) driven by compressed oxygen and inserted between the inspiratory limb of a circle anesthesia system and the endotracheal tube. The nebulizer delivered aerosol particles with a mass median diameter of 5.7 μ. To avoid residual contamination, the circle system was changed after completion of aerosol administration. *Ascaris* antigen was prepared by Sephadex filtration using the method of Mackler, Malley, and Amkraut (12). *Ascaris* protein, 30 μg of the purified extract, was placed in 10 ml of a vehicle solution and delivered as an aerosol over a 10-minute period.

The antigen aerosol vehicles for control and for lidocaine-treated experiments, respectively, were 0.9% saline and 4% lidocaine (Astra Pharmaceutical Products, Inc, Worchester, MA), which were isotonic and of approximately equal pH (5.5 to 6.5). In order to ensure that lidocaine-treated animals were protected from the start of challenge with *Ascaris* antigen aerosols, 4% lidocaine was also administered as a 10-minute pretreatment aerosol. In order to assess the effect of the aerosol itself, and also to allow for a lag in onset of drug effect, a 10-minute interval separated the pretreatment aerosol from the challenge aerosol. Control animals received a similar pretreatment aerosol employing 0.9% saline. Responses to *Ascaris* antigen challenge during treatment with lidocaine or saline aerosols were tested on separate days approximately 1 week apart.

In a separate series of experiments to assess the adequacy of reflex block following administration of the 10-minute lidocaine pretreatment aerosol, the same dogs were challenged with aerosols of citric acid. The citric acid aerosol was made up in distilled water and administered for 2 minutes. The most reactive animal was challenged with 3% citric acid and the remaining four animals with 10% citric acid. In separate weeks, the 2-minute citric acid challenge was delivered without preceding treatment or 2 minutes after completion of a lidocaine pretreatment aerosol.

R_L and C_{dyn} were measured in the control period and at 5-minute intervals after aerosol challenge. Post-challenge values in control and lidocaine-treated experiments were compared by *t*-test. The level of statistical significance used was $p < 0.05$.

For determination of blood lidocaine levels, a 2-ml sample of whole blood was added to a tube containing 30 ml of 1-chlorobutane and 1 ml of 0.1 M phosphate buffer (pH 7.4) with 50 units of heparin. After shaking for 10 minutes followed by centrifugation, a 25-ml portion of the organic layer was extracted into 2 ml of 1 N HCl. A 1.6-ml aliquot of the acid was then neutralized with 4 M phosphate buffer (pH 7.4) in a Reactivial (Pierce Chemical Co, Rockford, IL) and extracted into 25 μl of chloroform containing docosane (50 μg/ml) as the internal standard. Samples were

TABLE

Effect of Pretreatment Aerosols on Pulmonary Resistance (R_L) and Dynamic Compliance (C_{dyn})*

	R_L	C_{dyn}	Significance†
	cm H_2O/L/sec	*ml/cm H_2O*	
Before lidocaine aerosol	2.3 ± 0.5	148 ± 38	
After lidocaine aerosol	3.8 ± 1.3	119 ± 65	$p < 0.05$
Before saline aerosol	2.6 ± 0.4	127 ± 28	
After saline aerosol	3.0 ± 0.8	115 ± 23	NS

* Values are means ± SEM.

† Significance of aerosol-induced changes; NS, not statistically significant.

analyzed on a Hewlett-Packard 5830 gas chromatograph using flame ionization and a 1.75 m x 2 mm (ID) glass column packed with 1.5% OV-101 on Gas Chrom Q. The oven temperature was programmed at 10 C/min from 170 to 250 C. Standard curves were prepared for each experiment by adding lidocaine to dog blood; correlation coefficients for standard curves varied from 0.991 to 0.998.

Results

Response to Lidocaine and Saline Aerosols

Saline aerosols did not significantly alter mean values for R_L and C_{dyn} (Table), and the maximal change in R_L in individual experiments was less than 1 cm H_2O/L/sec. In contrast, lidocaine aerosols significantly increased mean R_L and decreased mean C_{dyn} (Table). In individual experiments, lidocaine aerosols increased R_L by at least 1 cm H_2O/L/sec in five of 10 trials; in these five, the increase in R_L averaged 3.0 cm H_2O/L/sec, ranging from 1.2 to 7.5. Lidocaine-induced increases in R_L were usually maximal immediately after completion of the pretreatment aerosol.

Protection against Citric Acid Challenge

In untreated control animals, inhalation of citric acid aerosols produced maximal effects on R_L and C_{dyn} 5 minutes after completion of the challenge aerosol (Fig 1). At that time, citric acid had significantly increased R_L from a prechallenge mean of 1.6 ± 0.4 (SEM) cm H_2O/L/sec to 10.6 ± 1.8 postchallenge, and it had significantly decreased C_{dyn} from 140 ± 27 ml/cm H_2O to 53 ± 8. After pretreatment with lidocaine aerosols, the citric acid challenge did not elicit statistically significant changes in either R_L or C_{dyn} (Fig 1).

Lack of Protection against Antigen-Challenge

Ascaris antigen aerosols elicited marked increases in R_L and decreases in C_{dyn} in both lidocaine- and saline-treated animals. These changes were maximal immediately after completion of the challenge aerosol and declined with half-lives of roughly 15 minutes (Fig 2). In control experiments, in which saline solution was used as the pretreatment aerosol and as the vehicle for the *Ascaris* antigen aerosol, R_L signifi-

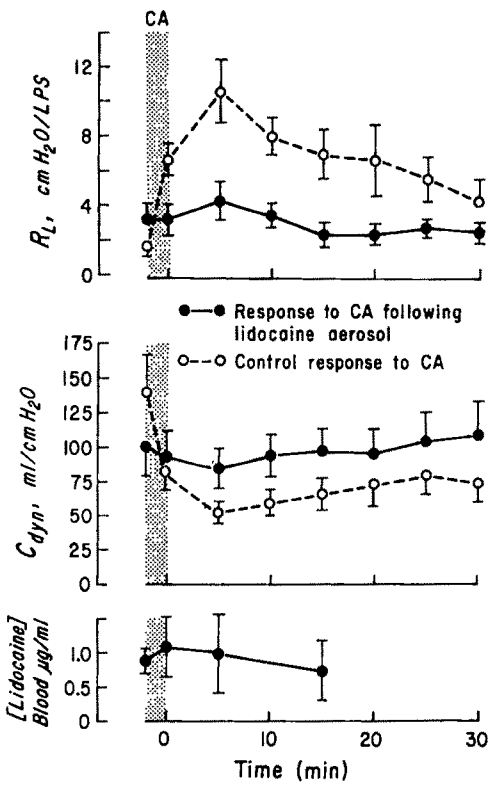


FIG 1. Response to citric acid (CA) aerosols in control experiments and following pretreatment with lidocaine aerosols. Each point shows mean ± SEM of five dogs. Shaded bar indicates period of challenge aerosol. Blood lidocaine levels are indicated in treated dogs.

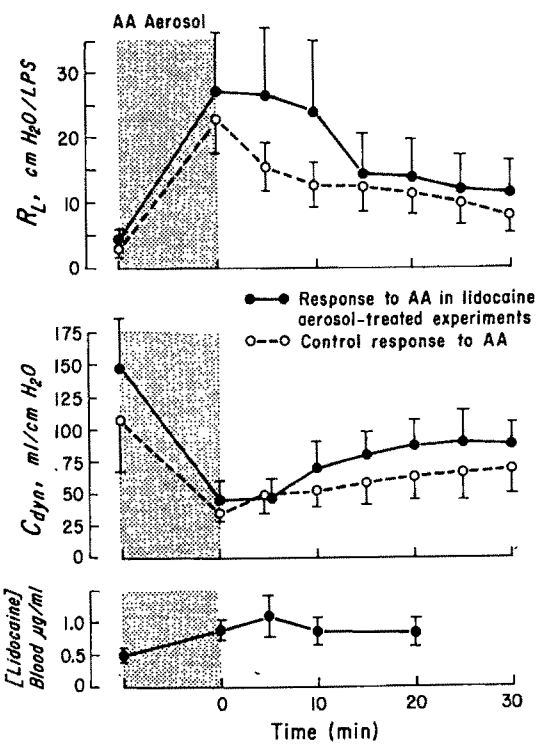


FIG 2. Response to *Ascaris* antigen (AA) aerosols in dogs treated with saline (control) or lidocaine aerosols. Each point shows mean ± SEM of five dogs. Shaded bar indicates period of challenge aerosol. Blood lidocaine levels are indicated in treated dogs.

cantly increased from a prechallenge mean of 2.9 ± 0.6 cm H_2O/L/sec to 22.8 ± 5.1 immediately postchallenge, and C_{dyn} decreased from 108 ± 41 ml/cm H_2O to 36 ± 8. When 4% lidocaine was employed as the pretreatment aerosol and as the vehicle for the *Ascaris* antigen aerosol, R_L significantly increased from a prechallenge mean of 4.2 ± 1.7 cm H_2O/L/sec to 26.9 ± 9.3 immediately postchallenge, and C_{dyn} decreased from 147 ± 43 ml/cm H_2O to 44 ± 15. There were no statistically significant differences in antigen-induced changes in R_L or C_{dyn} between lidocaine- and saline-treated animals.

Blood Lidocaine Levels

Blood lidocaine levels reached maximal values 5 minutes after completion of a lidocaine aerosol and were well sustained (Figs 1 and 2) for the next 15 minutes (the last blood sample obtained). Mean peak blood levels of lidocaine were 1.2 ± 0.4 and 1.1 ± 0.3 μg/ml during challenge with *Ascaris* antigen and citric acid, respectively. In individual experiments, peak lidocaine blood levels ranged from a low of 0.6 μg/ml to a high of 3.3 μg/ml.

Discussion

Our results show that lidocaine aerosols were able to prevent reflex bronchoconstriction, as elicited by the 2-minute citric acid challenge, but were entirely ineffective against antigen-induced bronchoconstriction. The response to antigen aerosols represents the effects of chemical mediators, which are released from sensitized cells on contact with antigen and which can act either directly on bronchi or by stimulation of sensory receptors with subsequent reflex bronchoconstriction (13). The role of reflex bronchoconstriction in experimental canine asthma is controversial (14, 15), but in the Basenji-Greyhound dogs large doses of atropine (0.2 mg/kg IV) (16) only slightly reduce the intensity of bronchoconstriction elicited by *Ascaris* antigen aerosols. Topical application of local anesthetics as aerosols interrupts irritant reflexes and, in addition, might produce other, more direct effects. In vitro studies have demonstrated that lidocaine, at concentrations approximately 100-fold higher than can be achieved safely in systemic blood, impairs mediator release (10) and directly relaxes airway smooth muscle (8, 9). High concentrations of lidocaine can be delivered to the lung during aerosol administration. Moreover, local anesthetics are concentrated in lung (17–19) and, conceivably, aerosol administration might produce high levels in cellular organelles such as mast cell granules.

To maximize the effect of lidocaine, we both pretreated with lidocaine aerosols and administered lidocaine by aerosol throughout the antigen challenge. Thus, before and during antigen challenge, we nebulized a total of 20 ml of lidocaine solution, containing 800 mg of drug, directly into the inspiratory limb of the circle anesthesia system just proximal to the endotracheal tube. Preliminary experiments with our apparatus indicate that approximately 75% of the nebulized dose is retained within the anesthesia circuit or lost into room air through the exhaust valve. Thus, the absorbed dose was roughly 200 mg, or 10 mg/kg, administered over a 30-minute period. Since this produced blood levels as high as 3 μg/ml in some animals, it is close to the maximal dose that can be safely administered. The complete lack of efficacy of lidocaine aerosols confirms the minor role of irritant reflexes in the Basenji-Greyhound response to antigen-aerosols, and demonstrates that administration of lidocaine by aerosol cannot achieve high enough tissue concentrations to impair mediator release significantly or relax bronchial smooth muscle directly.

Several recent studies have tested lidocaine aerosols in awake patients. In normal subjects, lidocaine aerosols produced little effect on pulmonary mechanics (20, 21). In contrast, in patients with reactive airway disease (22–24), lidocaine aerosols usually caused some degree of bronchoconstriction, which was reduced by atropine (24). Following the initial bronchoconstriction, a delayed bronchodilator effect was observed in some patients (23). Our dogs also showed bronchoconstrictor responses to lidocaine aerosols, but there was no evidence of protection against antigen-induced bronchoconstriction even though antigen challenge was begun 20 minutes after the start of the lidocaine pretreatment aerosol.

Our data indicate that lidocaine aerosols are only effective against reflex bronchoconstriction. Furthermore, in a previous study in the same experimental model (7), intravenous administration of lidocaine (mean blood level, 1.5 μg/ml) produced a marked reduction in reflex bronchoconstriction, which was almost as great as that produced in the present study by aerosol administration. Block of irritant reflexes by intravenously administered lidocaine probably represents a central nervous system effect, whereas reflex block after aerosol lidocaine results from both topical anesthesia and the systemic effect of absorbed drug. Since intravenous lidocaine (7) or atropine (16) produced a slight but consistent reduction in the

response to *Ascaris* antigen, the complete inefficacy of lidocaine aerosols against antigen challenge was unexpected. A possible explanation is that the slight protection afforded by reflex block was masked by local effects of lidocaine, unrelated to topical anesthesia, which exacerbated the bronchoconstrictor response to *Ascaris* antigen. We conclude that aerosol administration of lidocaine for the treatment of reactive airway disease offers little or no advantage over the intravenous route and probably should be avoided.

ACKNOWLEDGMENTS

The authors wish to thank A. Malley, PhD of the Oregon Regional Primate Center for purifying the *Ascaris* antigen, the Hudson Company for supplying the nebulizer, M. Lall and F. Cetinich for typing the manuscript, B. Bonn for help with chemical assays, and D. R. Morrow for help with animal experiments.

REFERENCES

1. Steinhaus JE, Howland DE. Intravenously administered lidocaine as a supplement to nitrous oxide thiobarbiturate anesthesia. Anesth Analg 1958;37:40–46.
2. Steinhaus JE, Gaskin L. A study of intravenous lidocaine as a suppressant of cough reflex. Anesthesiology 1963;24:285–290.
3. Poulton TJ, James FM. Cough suspension by lidocaine. Anesthesiology 1979;50:470–472.
4. Cross BA, Guz A, Jain SK, Archer S, Stevens J, Reynolds F. The effect of anesthesia of the airway in dog and man: a study of respiratory reflexes, sensations and lung mechanics. Clin Sci 1976;50:439–454.
5. Thomson NC. The effect of different pharmacological agents on respiratory reflexes in normal and asthmatic subjects. Clin Sci 1979;56:235–241.
6. Brandus V, Joffe S, Benoit CV, Wolff WI. Bronchial spasm during general anaesthesia. Can Anaesth Soc J 1970;17:269–274.
7. Downes H, Gerber N, Hirshman CA. Intravenous lignocaine in reflex and allergic bronchoconstriction. Br J Anaesth 1980;52:873–878.
8. Weiss EB, Anderson WH, O'Brien KP. The effect of a local anesthetic, lidocaine, on guinea pig trachealis muscle in vitro. Am Rev Respir Dis 1975;112:393–400.
9. Downes H, Loehning RW. Local anesthetic contracture and relaxation of airway smooth muscle. Anesthesiology 1977;47:430–436.
10. Weiss EB, Hargraves WA, Viswanath SG. The inhibitory action of lidocaine in anaphylaxis. Am Rev Respir Dis 1978;117:859–869.
11. Von Neergaard K, Wirz K. Die Messung der Strömungswiderstände in den Atemwegen des Menschen, insbesondere bei Asthma und Emphysem. Z Klin Med 1927;105:51–82.
12. Mackler B, Malley A, Amkraut AA. Antigen mediated transformation of rhesus lymphocytes in immediate and delayed hypersensitivity. Int Arch Allergy Appl Immunol 1971;41:765–777.
13. Drazen JM. Pulmonary physiological abnormalities in animal models of acute asthma. In: Lichtenstein LM, Austen KF, eds. Asthma: physiology, immunopharmacology and treatment. New York: Academic Press, 1977:249–262.
14. Gold WM, Kessler G-F, Yu DYC. Role of vagus nerves in experimental asthma in allergic dogs. J Appl Physiol 1972;33:719–725.
15. Krell RD, Chakrin LW, Wardell JR. The effect of cholinergic agents on a canine model of allergic asthma. J Allergy Clin Immunol 1976;58:19–30.
16. Downes H, Hirshman CA. The Basenji-Greyhound (B-G) dog model of asthma: role of irritant reflexes. Am Rev Respir Dis 1980;121:66.
17. Sung C-Y, Truant AP. The physiologic disposition of lidocaine and its comparison in some respects with procaine. J Pharmacol Exp Ther 1954;112:432–443.
18. Keenaghan JB, Boyes RN. The tissue distribution, metabolism and excretion of lidocaine in rats, guinea pigs, dogs, and man. J Pharmacol Exp Ther 1972;180:454–463.
19. Benowitz N, Forsyth RP, Melmon KL, Rowland M. Lidocaine disposition kinetics in monkey and man. 1. Prediction by a perfusion model. Clin Pharmacol Ther 1974;16:87–98.
20. Chaudhary BA, Speir WA. Effect of lidocaine anesthesia on pattern of ventilation and pulmonary function tests. South Med J 1979;72:1246–1251.
21. Gal TJ, Suratt PM. Resistance to breathing in healthy subjects following endotracheal intubation under topical anesthesia. Anesth Analg 1980;59:270–274.
22. Miller WC, Awe R. Effect of nebulized lidocaine on reactive airways. Am Rev Respir Dis 1975;111:739–741.
23. Weiss EB, Patwardhan AV. The response to lidocaine in bronchial asthma. Chest 1977;72:429–438.
24. Fish JE, Peterman VI. Effects of inhaled lidocaine on airway function in asthmatic subjects. Respiration 1979;37:201–207.

ANESTH ANALG
60:33-36, 1981

Cardiovascular Effects of Protamine Sulfate in Man

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CONAHAN, T. J., III, ANDREWS, R. W., AND MACVAUGH, H., III: Cardiovascular effects of protamine sulfate in man. Anesth Analg 1981;60:33-36.

The effect of protamine sulfate on several cardiovascular and biochemical variables was studied in man under clinical conditions. This study was performed to quantitate these effects in 15 adult patients who had undergone cardiopulmonary bypass for coronary artery bypass grafting. Protamine was administered in typical clinical doses (3 mg/kg) at typical clinical rates (total dose infused over 5 minutes). This infusion rate is greatly in excess of the 50 mg/10 min suggested in the protamine package insert. No statistically significant changes in mean arterial blood pressure, cardiac output, central venous pressure, total or ionized calcium, Pa_{O_2}, Pa_{CO_2}, pH, Na^+, or K^+ were found during or after administration of protamine sulfate. Hypotension was observed after administration of protamine to one patient, but no etiologic mechanism was apparent. Previous reports suggest cardiovascular depression by protamine in the dog, a species highly susceptible to these effects. Data obtained in man in this study do not corroborate the canine studies.

Key Words: BLOOD, coagulation: protamine; SURGERY: cardiovascular.

IT HAS BEEN presented as pharmacologic gospel that protamine sulfate, administered intravenously, decreases arterial blood pressure and cardiac output (CO) (1, 2). Most of the data supporting these teachings have been derived from animal studies, occasionally corroborated by clinical impression (1-6).

The package insert accompanying protamine sulfate cations against administration at a rate greater than 50 mg in 10 minutes. We have observed that in clinical situations, using protamine to antagonize the anticoagulant effect of heparin after cardiopulmonary bypass (CPB), the total dose of protamine (3 mg/kg) is usually administered in approximately 5 minutes. The total dose of 3 mg/kg is our standard amount, an acknowledged overdose based on previous studies (7). We designed a study to evaluate blood pressure and cardiac output after infusion of protamine at our usual rate. In addition, freshly prepared protamine solution (The Upjohn Co, Kalamazoo, MI) was compared with prepackaged protamine solution (Lilly and Co, Indianapolis, IN) to test a clinical impression that the freshly prepared solution caused more hypotension than the prepackaged solution.

Methods

This study was reviewed by the Human Studies Committee and met the standards in effect at the University of Pennsylvania at the time it was performed. Fifteen patients undergoing coronary artery bypass surgery were studied after discontinuation of CPB. The decision to study a particular patient was based on availability of equipment and personnel. No patient was excluded from this study because of age, physical status, severity of coronary disease, impairment of cardiac function, or intraoperative bleeding. Each patient had received heparin, 300 units/kg IV, intravenously before initiation of CPB. The type of protamine solution was chosen randomly and its identity was unknown to either the investigator or the anesthesiologist caring for the patient. Eight patients received Lilly protamine and seven received the Upjohn preparation.

Protamine sulfate was infused, as described below, into a peripheral vein after major bleeding from the

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Received from the Departments of Anesthesia and Surgery, Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania. Accepted for publication September 22, 1980. Portions of these data were presented at the Annual Meeting of The American Society of Anesthesiologists, New Orleans, LA, October 15-19, 1977.

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heart, grafts, and great vessels had been surgically corrected. Conditions during the 10-minute study period were maintained as close to a "steady state" as possible in a clinical situation. Further major surgical manipulations of the heart were delayed until all measurements had been completed. Transfusions were withheld and only minimal amounts of crystalloid were administered. No anesthetic or other drug with cardiovascular activity was administered. After completion of the measurements described below, the still heparinized contents of the CPB circuit and heparinized autologous blood were returned to the patient. Additional protamine was then administered to antagonize this heparin.

Arterial blood samples were drawn and cardiac output determined in duplicate at four times: (*a*) before administration of protamine; (*b*) 1 minute after cessation of an infusion of protamine (1 mg/kg) in 30 seconds; (*c*) 1 minute after cessation of a second infusion of protamine (2 mg/kg), producing a total protamine dose of 3 mg/kg, administered over 3 to 5 minutes; and (*d*) 5 minutes after cessation of infusion in *c*. Arterial and central venous pressures were recorded on a continuous chart recorder. Pulmonary artery pressure was not recorded in all patients. Cardiac output was measured in duplicate by the thermodilution technique. Arterial blood samples were analyzed for P_{O_2}, P_{CO_2}, and pH utilizing an Instrumentation Laboratories (Andover, MA) model 127 system. Levels of serum sodium and potassium were measured using an Orion SS30 unit (Orion Research, Inc, Cambridge, MA). Total calcium (Ca^{tot}) was determined with the Corning fluorescent titration system (Corning Glassworks Co, Corning, NY). Ionized calcium (Ca^{2+}) was measured with the Orion model SS20 electrode system. Differences between protamine preparations were sought by comparing, at times B, C, and D, changes from control in mean arterial blood pressure (MABP), cardiac output (CO), Ca^{2+}, and Ca^{tot}. Statistical significance ($p < 0.05$) was tested using the unpaired *t*-test.

Data from both groups were combined and analysis of variance used to evaluate protamine effect on CO, MABP, central venous pressure (CVP), Ca^{tot}, Ca^{2+}, pH, P_{O_2}, P_{CO_2}, sodium, and potassium; $p < 0.05$ was accepted as significant.

Results

The two groups of patients were similar in age, weight, protamine dose, estimated blood loss, and time from end of CPB to end of operation (a crude index of bleeding after CPB) as summarized in Table 1. Comparison of the two preparations of protamine showed no difference in their effects on MABP, CO, Ca^{2+}, or Ca^{tot} (Table 2). Thus, we could not confirm our clinical impression that freshly prepared protamine solution caused more hypotension.

When we could detect no difference between the two preparations of protamine sulfate, we combined the data from both groups of patients and compared the effects of protamine on the several variables, using the group as its own control (Table 3).

We detected no statistically significant decrease in MABP following administration of protamine, although individual changes ranged from a 40 torr decrease to an 18 torr increase. Data from one patient (Upjohn group) were eliminated from the study after his anesthesiologist elected to administer vasopressors because of hypotension during the second protamine infusion of the study period. Data from that patient obtained before administration of the vasopressor (including the MABP that prompted intervention) are included.

Cardiac output appeared unaffected by administration of protamine. The variations in cardiac output from the control values reported in Table 3 are within the 10% error in the method (8). Similarly, we could not detect a meaningful change in CVP, Ca^{2+}, or Ca^{tot}, nor in the other variables studied after administration of up to 3 mg/kg of protamine. Table 3 summarizes the data for MABP, CO, CVP, Ca^{2+}, and Ca^{tot}.

Discussion

Jastrzebski et al (9) have reported one of the few studies of cardiovascular responses to the intravenous administration of protamine in man. They infused 6 mg/kg of protamine intravenously over approximately 5 minutes. They commented (9) that "the femoral artery pressure fell in most patients," but did not record data to substantiate the observation. Within 5 minutes after protamine infusion, the pressure had "usually returned to preinjection levels." The Jastrzebski et al study did not demonstrate a statistically significant decrease in cardiac index after protamine administration. Continuous recording of the arterial pressure did not demonstrate consistent hypotension in our study. We also could detect no statistically significant change in cardiac output after administration of protamine.

Most of the evidence of cardiovascular depression by protamine appears to have been gathered in canine studies. Jaques (3) found that of all the species studied, the canine cardiovascular system was the most vul-

TABLE 1

Characteristics of Study Population*

	Age	Weight	Body surface area	Estimated blood loss	Operating time after CPB
	yr	*kg*	m^2	*ml*	*min*
Lilly (N = 8)	53.8 ± 9.3	79.3 ± 13.8	1.91 ± 0.28	830 ± 420	111 ± 18
Upjohn (N = 7)	53.7 ± 9.6	74.1 ± 9.6	1.87 ± 0.15	532 ± 463	94 ± 17

* Values are means ± SD. No statistically significant ($p < 0.05$) differences detected between the groups.

TABLE 2

Comparison of Effects of Protamine Sulfate Preparations*

Change in	1 min after 1 mg/kg dose	1 min after total dose (3 mg/kg) administered	5 min after total dose (3 mg/kg) administered
MABP (torr)			
Lilly	−2.6 ± 10.4 (n = 8)	−6.4 ± 9.8 (n = 8)	−4.3 ± 10.8 (n = 8)
Upjohn	+0.4 ± 7.5 (n = 7)	−8.3 ± 19.9 (n = 7)	+1.4 ± 13.3 (n = 6)†
CO (L/min)			
Lilly	−0.23 ± 0.49 (n = 8)	−0.51 ± 0.56 (n = 8)	−0.64 ± 0.97 (n = 8)
Upjohn	+0.02 ± 0.17 (n = 6)‡	−0.28 ± 0.48 (n = 6)†	−0.32 ± 0.93 (n = 6)†
Ca^{2+} (meq/L)			
Lilly	−0.06 ± 0.19 (n = 8)	−0.10 ± 0.19 (n = 8)	−0.10 ± 0.19 (n = 8)
Upjohn	−0.06 ± 0.14 (n = 7)	−0.12 ± 0.10 (N = 7)	−0.08 ± 0.13 (n = 6)†
Ca^{tot} (meq/L)			
Lilly	−0.17 ± 0.14 (n = 8)	−0.23 ± 0.19 (n = 8)	−0.25 ± 0.27 (n = 8)
Upjohn	−0.16 ± 0.20 (n = 7)	−0.33 ± 0.20 (n = 7)	−0.31 ± 0.18 (n = 6)†

* Values are means ± SD. No statistically significant ($p < 0.05$) differences detected.

† Data from one patient (A) deleted because of pharmacologic intervention. See text.

‡ CO from one patient not available from this pericd because of equipment malfunction. Data from patient A are included.

TABLE 3

Effects of Protamine Sulfate (Lilly and Upjohn Groups Combined)*

	Control	1 min after 1 mg/kg dose	1 min after total dose (3 mg/kg)	5 min after total dose (3 mg/kg)
MABP (torr)	88.8 ± 16.3	87.6 ± 18.4	81.8 ± 22.6	86.4 ± 18.0
N	15	15	15	14†
C.O. (L/min)	5.05 ± 1.49	4.99 ± 1.46	4.66 ± 1.32	4.57 ± 1.37
N	15	14‡	14†	14†
CVP (torr)	12.7 ± 5.0	12.1 ± 4.9	12.1 ± 5.4	13.0 ± 5.2
N	15	15	15	14†
Ca^{2+} (meq/L)	1.77 ± 0.19	1.71 ± 0.15	1.66 ± 0.16	1.67 ± 0.17
N	15	15	15	14†
Ca^{tot} (meq/L)	3.84 ± 0.45	3.67 ± 0.43	3.56 ± 0.36	3.56 ± 0.38
N	15	15	15	14†

* Values are means ± SD. No statistically significant ($p < 0.05$) differences detected.

† Data from one patient (A) excluded after pharmacologic intervention. See text.

‡ Data from one patient unavailable because of equipment malfunction. Data from patient A are included.

nerable to protamine. Most investigators have continued to study protamine in the dog, and have thus been testing the "worst possible case."

Hurt et al (4) reported hypotension of varying degree in all 26 dogs receiving protamine in their study. They speculated that the effect was due to arteriolar dilation. Goldman et al (2) found a decrease in both cardiac output and systemic arterial pressure in dogs associated with the intravenous administration of protamine. They found evidence of both vasodilation and decreased myocardial contractility. The study by Gourin et al (5) of protamine administration to dogs demonstrated systemic arterial hypotension and decreased systemic arterial blood flow after the drug was given. These authors also demonstrated that the arterial hypotension associated with protamine

infusion could be minimized by the intravenous administration of fluids before and during protamine administration. Gourin et al (5) reported anecdotally that, by similar use of intravenous fluids in patients, it became possible to prevent arterial hypotension during and after protamine sulfate administration in humans.

Fadali et al (1) attempted to elucidate the mechanism responsible for cardiovascular depression by protamine in dogs. In separate groups of animals they blocked alpha- and beta-adrenergic receptors, the autonomic ganglia, and the adrenal medulla. In another group they depleted endogenous histamine. None of these maneuvers blocked the dogs' vascular responses to protamine. Measures of myocardial contractility (dp/dt, V_{max}) were also decreased after protamine administration. They isolated the vascular tree during CPB and still detected vasodilation in response to protamine infusion. Fadali, et al (1) concluded that protamine has both myocardial and peripheral vascular depressant actions. Gourin et al (6) studied myocardial contractility in a more rigorously controlled setting, with the preload held constant and found no depressant effect of protamine on left ventricular pressure or on dp/dt.

Our data, obtained in humans under clinical con ditions, suggest that protamine normally has little, if any, effect on arterial blood pressure or on cardiac output. Every physician who administers protamine has anecdotal evidence that the drug occasionally causes some harmful effect to the cardiovascular system. We set out to document that and could not. We can, however, contribute our own anecdote about the patient referred to earlier, whose anesthesiologist judged it necessary to administer epinephrine and calcium to treat hypotension during protamine infusion. This patient had a low (6 torr) CVP at the start of the protamine infusion. This low CVP may well have reflected hypovolemia that combined with some otherwise undetected cardiovascular depression to produce hypotension. We could find no statistical correlation between CVP and change in either MABP or cardiac output at any time during or after protamine administration (correlation coefficients ranged from −0.182 to +0.370).

Protamine is capable of causing hypocalcemia in some animals (10). Nahrwold and Denlinger (11) found that in man serum levels of Ca^{2+} decreased during infusion of protamine, 4.5 mg/kg. We could not duplicate that finding using our usual clinical dose of protamine, 3 mg/kg. We also found no change in Ca^{tot}.

In this study we measured the effects of typical clinical rates of administration of protamine on cardiac output and arterial blood pressure in patients during surgery and anesthesia. We found, on the average, no effect of protamine on these parameters. We speculate that in the one patient in whom we detected clinically significant hypotension, low CVP reflected hypovolemia. His transient hypotension may have been the result of some minimal, otherwise undetectable, cardiovascular action of protamine combined with the hypovolemia, or it may have been entirely unrelated to either. A recent report (12) describes an apparent anaphylactic response to protamine—in a patient potentially sensitized to protamine. Neither the associated signs nor the time course of the hypotension suggested a similar event in our patient.

On the basis of our data, and that of Jastrzebski et al (9), we conclude that the cardiovascular effects of protamine sulfate appear to be more benign in man than in the dog. We have not demonstrated the fastest safe rate of protamine administration but believe that we have shown that, on the average, the drug is not a cardiovascular depressant.

REFERENCES

1. Fadali MA, Ledbetter M, Papacostas CA, Duke LJ, Lemole GM. Mechanism responsible for the cardiovascular depressant effect of protamine sulfate. Ann Surg 1974;180:232–5.
2. Goldman BS, Joison J, Austin WG. Cardiovascular effects of protamine sulfate. Ann Thorac Surg 1969;7:459–71.
3. Jaques LB. A study of the toxicity of the protamine (salmine). Br J Pharmacol 1949;4:135–44.
4. Hurt R, Perkins HA, Osborn JJ, Gerbode F. The neutralization of heparin by protamine in extracorporeal circulation. J Thorac Surg 1956;32:612–9.
5. Gourin A, Streisand RL, Greineder JK, Stuckey JH. Protamine sulfate administration and the cardiovascular system. J Thorac Cardiovasc Surg 1971;62:193–204.
6. Gourin A, Streisand RL, Stuckey JH. Total cardiopulmonary bypass, myocardial contractility and the administration of protamine sulfate. J Thorac Cardiovasc Surg 1971;61:160–6.
7. Ellison N, Beatty CP, Blake DR, Wurzel HA, MacVaugh H. Heparin rebound. J Thorac Cardiovasc Surg 1974;67:723–9.
8. Weil MH. Measurement of cardiac output (editorial). Crit Care Med 1977;5:117–9.
9. Jastrzebski J, Sykes MK, Woods DG. Cardiorespiratory effects of protamine after cardiopulmonary bypass in man. Thorax 1974;29:534–8.
10. Johnston CL Jr, Grinnan EL, Wilson HC, Boder GB. Protamine-induced hypocalcemia. Endocrinology 1970;87:211–7.
11. Nahrwold ML, Denlinger JK. The effects of heparin and protamine infusion on serum ionized calcium in anesthetized man. Anesthesiol Rev 1976;3:24–5.
12. Moorthy SS, Pond W, Rowland RG. Severe circulatory shock following protamine (an anaphylactic reaction). Anesth Analg 1980;59:77–8.

ANESTH ANALG
60:37-40, 1981

Effects of Atropine, Glycopyrrolate, and Cimetidine on Gastric Secretions in Morbidly Obese Patients

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WILSON, S. L., MANTENA, N. R., AND HALVERSON, J. D.: Effects of atropine, glycopyrolate, and cimetidine on gastric secretions in morbidly obese patients. Anesth Analg 1981;60:37-40.

Gastric volume and pH were studied immediately after induction of anesthesia and endotracheal intubation in 40 morbidly obese patients undergoing gastric bypass procedures. Of 14 patients receiving intramuscular atropine (0.6 mg) preoperatively, 67% had gastric pH values < 2.5; 33% of these patients had both a gastric pH <2.5 and a volume >20 ml. When the drug administered was intramuscular glycopyrrolate (0.3 mg), 62% of the patients had gastric pH values <2.5; 30% had both gastric pH values < 2.5 and volumes >20 ml. Differences between the two drugs were not significant. Thirteen patients received cimetidine orally at midnight preoperatively and again 2 to 4 hours before the induction of anesthesia. Patients in this group had gastric pH values that were significantly higher than those observed in patients given anticholinergic drugs. Only 15% had gastric pH values <2.5. Gastric volumes observed in patients receiving cimetidine were not significantly different from those receiving anticholinergic drugs. Whereas only 7.9% of patients receiving cimetidine had both low pH values and gastric volumes >20 ml, this was not statistically different from the observations made in patients receiving atropine or glycopyrrolate. Despite this, it is concluded that cimetidine administered before the induction of anesthesia in morbidly obese patients may reduce the high risk of aspiration pneumonitis in such patients.

Key Words: PARASYMPATHETIC NERVOUS SYSTEM: atropine and glycopyrrolate; HISTAMINE: cimetidine; GASTROINTESTINAL TRACT: stomach; COMPLICATIONS: obesity.

ASPIRATION and resultant chemical pneumonitis remain a serious hazard associated with the administration of anesthesia (1). Vaughn et al (2) demonstrated that the morbidly obese patient is at significantly greater risk of aspiration than the non-obese patient. Anticholinergic drugs are commonly used to reduce volume and acidity of gastric secretions. Glycopyrrolate has been shown to be superior to atropine in this regard in pediatric patients (3). The histamine H_2 receptor antagonist, cimetidine (Tagamet), has been shown to increase gastric pH in non-obese adults (4). The purpose of this study was to compare the effectiveness of glycopyrrolate, atropine, and cimetidine in increasing gastric fluid pH and reducing volume in obese patients.

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Received from the Departments of Anesthesiology and Surgery, Washington University School of Medicine, St. Louis, Missouri. Accepted for publication October 5, 1980.
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Methods and Materials

The population investigated consisted of 40 morbidly obese patients scheduled for gastric bypass procedures in a study protocol approved by the Human Studies Committee at Washington University School of Medicine. No patient was receiving drugs known to influence gastric acidity or volume. All patients had preoperative upper gastrointestinal series, radiographs, and gastroscopy. None had pathology associated with hyperacidity.

The patients were divided randomly into three groups depending on the type of medication administered preoperatively: group I (14 patients) received atropine, 0.6 mg IM; group II (13 patients) received glycopyrrolate, 0.3 mg IM; and group III (13 patients) received cimetidine, 300 mg orally, at midnight and 300 mg orally at 6 a.m. Atropine and glycopyrrolate were administered on call for the operating room allowing a minimum of 45 minutes between administration of the drug and induction of anesthesia. Cimetidine was administered not only at midnight but also at 6 a.m. to allow 60 to 90 minutes to elapse between the administration of the second dose of

drug and the induction of anesthesia, thereby ensuring peak drug effectiveness (5).

Oxygen was administered for 3 minutes before induction of anesthesia. Drugs were administered on a milligram per kilogram lean body weight basis, where ideal body weight and lean body weight were assumed equal. Thiopental (4 mg/kg) was given intravenously followed by succinylcholine (1.5 mg/kg). Following endotracheal intubation with a cuffed tube, ventilation was controlled with a tidal volume of 15 ml/kg, eight times per minute. Pancuronium (0.1 mg/kg) was administered and anesthesia was maintained with Innovar, fentanyl, and nitrous oxide:oxygen, 60%:40%. Following induction, an 18-gauge French sump-type nasogastric tube was placed and gastric contents collected for measurements of pH and volume. Later the nasogastric tube was positioned in various areas of the stomach by the operating surgeon to determine whether the volume collected immediately following induction of anesthesia represented total gastric volume. Gastric fluid pH was determined both by use of a standard pH meter and by Color-pHast indicator sticks (EM Laboratories, Inc, Elmsford, NY).

Data were analyzed using the chi-square test. A p value less than 0.05 was considered statistically significant.

Results

The three groups were statistically similar in age, weight, height, and sex (Table 1). Gastric fluid pH values were similar with both methods used to measure pH. In no case was the obtained volume of gastric fluid increased following repositioning of the nasogastric tube after the abdomen was opened.

No significant difference was noted between atropine and glycopyrrolate in their effects on gastric volume and pH (Table 2). When atropine was administered, gastric volume was greater than 20 ml in 43% of the patients and pH was less than 2.5 in 67%. When glycopyrrolate was administered, these values were 39% and 62%, respectively. The mean time between administration of atropine or glycopyrrolate and the collection of gastric samples was 111 ± 9.3 minutes following atropine and 111 ± 7.5 minutes following glycopyrrolate.

The frequency of gastric pH values less than 2.5 was significantly less in patients receiving cimetidine than in patients receiving either atropine or glycopyrrolate ($p < 0.01$) (Table 2). Only 15% of patients given cimetidine fell into the low pH category. On the other hand, 23% of the patients given cimetidine had gastric volumes of more than 20 ml, not significantly different from values for patients given atropine or glycopyrrolate. The mean time between administration of cimetidine at 6 a.m. and sample collection was 181 ± 10.5 minutes.

If one looks at the frequency with which gastric pH was less than 2.5 and volume was more than 20 ml, it is seen that this combination of findings occurred in 33% of patients receiving atropine and in 30% of those receiving glycopyrrolate, but in only 7.9% of those receiving cimetidine (Table 2). The difference between cimetidine on the one hand and atropine or glycopyrrolate on the other was not statistically significant at the 0.05 level.

A fourth group of four patients was originally a part of our protocol. This group received no preanesthetic medication. In each patient gastric pH was found to be $\ll 2.5$ with a mean value of 1.3 ± 0.1 and a range of 1.0 to 1.6 and gastric volume was $\gg 20$ ml with a mean of 56.5 ± 4.5 and a range of 35 to 72. In view of the high risk of aspiration previously noted in these obese patients and the dramatic results seen with cimetidine, it was elected not to study this control group further.

Discussion

It has been shown that aspiration pneumonitis is most likely to occur when the pH of the aspirate is less than 2.5 with a volume of more than 20 to 25 ml (6–8).

Vaughn et al (2) demonstrated a significant difference in both pH and volume on obese and nonobese patients, with 75% of the obese patients appearing to be at risk of aspiration pneumonitis because of gastric pH values less than 2.5 and volume more than 25 ml.

TABLE 1

Physical Characteristics of Patient Population*

	Patient no.	Sex (M/F)	Age	Weight	Height
				kg	*cm*
Atropine	14	0/14	34.9 ± 2.42	129.4 ± 4.94	164.3 ± 1.13
Glycopyrrolate	13	1/12	32.2 ± 1.69	134.9 ± 5.91	167.9 ± 2.2
Cimetidine	13	1/12	30.8 ± 2.62	121.6 ± 4.76	166.0 ± 1.88

* Values are means ± SE.

TABLE 2
Characteristics of Gastric Secretions*

	pH (range)	Volume (range)	pH <2.5		Volume >20 ml		Combination pH >2.5 and volume <20 ml	
			No.	%	No.	%	No.	%
		ml	†					
Atropine (N = 14)	2.7 ± 0.6 (1–8.0)	25.0 ± 6.7 (0–62)	8/12	67	6/14	43	4/12	33
Glycopyrrolate (N = 13)	2.4 ± 0.4 (1–7.0)	21.8 ± 5.1 (2–55)	8/13	62	6/13	39	4/13	30
Cimetidine (N = 13)	5.0 ± 0.6 (1.3–8.0)	15.8 ± 4.5 (2–60)	2/13	15	3/13	23	1/13	7.9
			$P < 0.01$		NS		NS $0.05 < p < 0.1$	

* Values are means ± SE.
† Two of the patients receiving atropine had insufficient volume (<0.5 ml) aspirated to check pH.

None of their nonobese patients were similarly at risk. Neither anticholinergics nor histamine H_2 receptor blockers were administered to these patients.

Stoelting (8) compared the effects of intramuscular atropine, 0.4 mg, and glycopyrrolate, 0.2 mg, given before surgery in nonobese adult patients. Both groups received morphine intramuscularly before anesthesia. A control group received morphine alone. The data indicated that 16% to 17% of these fasting patients were at risk of aspiration pneumonitis because of a combination of gastric pH values less than 2.5 and gastric volumes more than 20 ml. Risk was not decreased by inclusion of atropine or glycopyrrolate in the preanesthetic medication.

Applying the above criteria of risk to our own data, the percentage of morbidly obese patients at risk was 30% to 33%, with no difference noted between those patients given atropine and those given glycopyrrolate intramuscularly in doses of 0.6 mg and 0.3 mg, respectively. Although a significant difference between atropine and glycopyrrolate on gastric pH and volume has been reported in pediatric patients (3), this is not the case in either the morbidly obese adult nor the nonobese adult (8).

Cimetidine, a histamine H_2 receptor antagonist, has been shown to decrease acid output signficantly in duodenal ulcer patients (9). Because of its ability to decrease gastric pH, cimetidine has been used as a part of preanesthetic medication. Earlier studies (4, 10) have shown that cimetidine increases gastric pH significantly when given orally before anesthesia. In one study 91.3% of cimetidine-treated patients vs 29.7% of untreated patients and, in another study, 84% of cimetidine-treated patients vs 40% of untreated patients had pH values greater than 2.5. There was, however, no statistically significant effect of cimetidine on gastric volume in either study.

In our study, 85% of the patients given oral cimetidine had gastric pH values above 2.5, whereas, only 33% and 38% of patients given atropine and glycopyrrolate, respectively, had pH values above 2.5. Gastric volume was similar after all three drugs—atropine, glycopyrrolate, and cimetidine. Only 7.9% of the patients given cimetidine fell into the high risk category with gastric pH less than 2.5 and volumes more than 20 ml. Previous studies (2) have demonstrated that 75% of obese patients are at risk by these criteria.

Cimetidine is also available in parenteral form and now has Food and Drug Administration approval for intramuscular and intravenous use. Several recent studies have addressed the question of what effect parenteral cimetidine has on gastric volume and pH into nonobese patients. Coombs et al (11) noted a significant time-dependent increase in gastric pH and, in addition, a decline in gastric volume in patients given cimetidine intravenously 15, 30, 45, and 60 minutes before induction of anesthesia.

Maliniak and Vakil (12) compared intramuscular glycopyrrolate with intravenous cimetidine and found cimetidine significantly superior in increasing pH, but not different from glycopyrrolate in its effect on volume.

Toung and Cameron (13), in a study remarkably similar to our own, compared the effects of atropine, glycopyrrolate, and oral plus intravenous cimetidine on gastric pH and volume in nonobese neurosurgical patients undergoing craniotomy for space-occupying lesions. Their results were similar to our own in that 93% of cimetidine-treated patients had gastric pH

values >2.5. Also, cimetidine-treated patients had significantly greater pH values than did patients treated with anticholinergic drugs. On the other hand, they noted a significant difference between atropine and glycopyrrolate, glycopyrrolate proving more often to be associated with gastric pH values >2.5 and volumes <25 ml. In addition, their data showed cimetidine significantly different from atropine with respect to gastric volume, but not different from glycopyrrolate. Gastric volumes less than 25 ml were observed in 82% of glycopyrrolate-treated patients, 89% of the cimetidine group, and in only 43% of the atropine-treated group.

Finally, comparisons of the effects of oral vs intramuscular cimetidine (14) have shown the intramuscular route to be superior to the oral route in terms of yielding higher gastric pH values. It remains to be shown whether parenteral administration of cimetidine is more effective than oral administration in the obese patient; such a study is currently underway.

A criticism of our study, as well as the others cited, is the uncertainty of the exact location of the gastric tube at the time of collection. We feel comfortable that the samples collected were representative of the true values of gastric volume at the time of induction of anesthesia, since in no case was further volume added when the gastric tube was repositioned by the operating surgeon.

In conclusion, our data indicate that in morbidly obese patients, a high risk group for aspiration pneumonitis, there is no beneficial effect on gastric pH and volume associated with administering glycopyrrolate as opposed to atropine. In contrast, cimetidine, 300 mg, administered orally at midnight and repeated with a sip of water 2 to 4 hours before surgery is highly effective in increasing gastric pH values and, therefore, may be effective in reducing the risk of aspiration pneumonitis in such patients.

ACKNOWLEDGMENT

We are indebted to the Washington University School of Medicine, Department of Biostatistics, for assistance in the statistical analysis.

REFERENCES

1. Stark DC. Aspiration in the surgical patient. In: Roberts R, ed. International Anesthesiology Clinics, Vol 15, No 1, Pulmonary Aspiration. Boston: Little, Brown and Co, 1977;13.
2. Vaughn RW, Bauer S, Wise L. Volume and pH of gastric juice in obese patients. Anesthesiology 1975;43:686–689.
3. Salem MR, Wong AY, Mani M, Bennett EJ, Toyama T. Premedicant drugs and gastric juice pH and volume in pediatric patients. Anesthesiology 1976;44:216–219.
4. Stoelting R. Gastric fluid pH in patients receiving cimetidine. Anesth Analg 1978;57:675–677.
5. Henn RW, Isenberg JI, Maxwell V, Sturdevant RAL. Inhibition of gastric acid secretion by cimetidine in patients with duodenal ulcer. N Engl J Med 1975;293:371–375.
6. Teabeaut JR. Aspiration of gastric contents: an experimental study. Am J Pathol 1952;28:51–62.
7. Roberts RB, Shirley MA. Reducing the risk of acid aspiration during cesarean section. Anesth Analg 1974;53:859–868.
8. Stoelting RK. Responses to atropine, glycopyrrolate and Riopan of gastric fluid pH and volume in adult patients. Anesthesiology 1978;48:367–369.
9. Schlippert W. Cimetidine H_2 receptor blockade in gastrointestinal disease. Arch Intern Med 1978;138:1257–1260.
10. Husemeyer RP, Davenport HT, Rajhsekaran T. Cimetidine for reducing acidity of gastric contents in elective surgery. Br J Anaesth 1978;50:1080.
11. Coombs DW, Hooper D, Colton T. Pre-anesthetic cimetidine alteration of gastric fluid volume and pH. Anesth Analg 1979;58:183–188.
12. Maliniak K, Vakil AH. Pre-anesthetic cimetidine and gastric pH. Anesth Analg 1979;58:309–313.
13. Toung T, Cameron JT. Cimetidine as a pre-operative medication to reduce the complications of aspiration of gastric contents. Surgery 1980;87:205–208.
14. Weber L, Hirshman CA. Cimetidine for prophylaxis of aspiration pneumonitis: comparison of intramuscular and oral dosage schedules. Anesth Analg 1979;58:426–427.

ANESTH ANALG
60:41-45, 1981

Anoxic Cerebral Potassium Accumulation Reduced by Phenytoin: Mechanism of Cerebral Protection?

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ARTRU, A. A., AND MICHENFELDER, J. D.: Anoxic cerebral potassium accumulation reduced by phenytoin: mechanism of cerebral protection? Anesth Analg 1981;60:41-45.

Results from a previous study suggested that the cerebral protective effect of phenytoin (PNT) might be linked to its ability to reduce cerebrospinal fluid potassium (K^+) accumulation during anoxia. In the present study two PNT doses (50 and 150 mg/kg) were examined to determine the ability of PNT to reduce cerebrospinal fluid K^+ in cisterna magna samples after 10 and 20 minutes of circulatory arrest. Also examined were two other protective treatments (pentobarbital, 33 mg/kg, and hypothermia to 35 C) which, in the hypoxic ($F_{I_{O_2}} = 0.05$) mouse, provide cerebral protection equivalent to PNT, 50 mg/kg. Both PNT doses significantly reduced cerebrospinal fluid K^+ accumulation and tended to do so in a dose-related manner, similar to the dose-related cerebral protective effect of PNT. PNT, 50 mg/kg, reduced K^+ accumulation more effectively than either pentobarbital or hypothermia, whose protective effects are likely explained by a different mechanism (i.e., reduced cerebral metabolic rate). These data support the hypothesis that PNT-induced cerebral protection may be linked to its effect on cerebral K^+ accumulation.

Key Words: PHARMACOLOGY: phenytoin; BRAIN: anoxia.

PHENYTOIN (PNT)-induced cerebral protection has been reported in numerous mammalian species during various conditions of reduced oxygen delivery (e.g., hypoxemia (1), global ischemia (2), anoxia (3), and incomplete ischemia (4)). In previous studies from this laboratory (5) we also observed a protective effect, and in addition found that PNT reduced cerebral blood flow, but did not change the cerebral metabolic rate for oxygen (CMR_{O_2}) in normoxic dogs, and only weakly attenuated hypoxemia convulsive activity in mice. Thus, the means by which the cerebral protective effects of other agents and conditions have commonly been explained—increased oxygen delivery, decreased oxygen utilization, or anticonvulsant activity—cannot explain PNT-induced cerebral protection. We also reported that PNT reduced the rate of accumulation of cisternal cerebrospinal fluid potassium ($[K^+]_{CSF}$) after induced circulatory arrest. On the basis that an increase in cerebral extracellular K^+ may aggravate the effects of reduced O_2 delivery (2, 6-8), we suggested that the ability of PNT to decrease $[K^+]_{CSF}$ accumulation may be linked to its protective effect.

The present study was designed to examine the ability of PNT to reduce cerebral $[K^+]_{CSF}$ accumulation, and to compare that phenomenon to the effects of two other recognized cerebral protective modalities—pentobarbital (PTB) and hypothermia. Previously the effects of PNT, PTB, and hypothermia on $[K^+]_{CSF}$ have only been individually reported in separate models and in different species (5, 6, 9). Two PNT doses were studied to determine whether PNT would exhibit a dose-related effect for decreasing $[K^+]_{CSF}$ accumulation similar to its dose-related effect for providing cerebral protection.

Methods

The subjects were 36 unmedicated, New Zealand White rabbits (weighing 3.5 to 5.0 kg) given free access to food pellets and tap water. Anesthesia was induced with 1% halothane and 60% nitrous oxide in oxygen. Intravenous administration of succinylcholine, 5 to 10 mg, as a bolus injection, followed by infusion of 25 to 50 mg/hr facilitated intubation and

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Supported in part by National Institutes of Health, Public Health Service, Research Grant NS-7507.

Received from the Department of Anesthesiology, University of Washington School of Medicine, Seattle, Washington, and the Department of Anesthesiology, Mayo Medical School, Rochester, Minnesota. Accepted for publication October 6, 1980.

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maintained relaxation. Ventilation was controlled with a Harvard pump (Harvard Apparatus Co, Inc, Millis, MA) and adjusted along with the inspired oxygen concentration to maintain serial blood gases (IL electrodes (Instrumentation Laboratory, Inc, Boston, MA) 37 C) at Pa_{O_2} 147 ± 6 mm Hg (mean ± SEM) and Pa_{CO_2} 39 ± 1 mm Hg. With the animal in the lateral position, the right femoral vein was cannulated for fluid and drug administration. The right femoral artery was cannulated for arterial blood sampling for blood gas analyses, buffer base determination, and continuous monitoring of systemic and mean arterial pressure and heart rate. Skin edges at the incision site were infiltrated with 1% lidocaine. The animal was then turned to the prone position. Biparietal electrodes were placed for electroencephalograph (EEG) monitoring, and a midline incision made over the occiput and posterior neck muscles—the site for subsequent CSF sampling. Skin edges at this site were also infiltrated with 1% lidocaine. The total lidocaine dose used was 2 to 4 mg/kg. Pharyngeal temperature was monitored by a thermistor probe and maintained near 38 C by heat lamps or ice packs.

The concentration of halothane was then lowered to less than 0.1%. When stable baseline measurements had been established (at least 20 minutes later) systemic values were determined and six animals randomly assigned to each of six groups. In the control group, anesthesia was maintained with $O_2/N_2O/<$ 0.1% halothane for 50 minutes. In a second group anesthesia was maintained with $O_2/N_2/<$ 0.1% halothane while PNT 150 mg/kg in the commerical vehicle was administered intravenously over 50 minutes. (The commercial vehicle for PNT is 40% propylene glycol and 10% alcohol in water buffered to pH 12 with sodium hydroxide.) In a third group anesthesia was maintained with $O_2/N_2/<$ 0.1% halothane while the commercial vehicle for PNT, in an amount equivalent to that in a dose of 150 mg/kg of PNT, was administered intravenously over 50 minutes. Anesthesia in the three remaining groups was maintained with $O_2/N_2/<$ 0.1% halothane while "equiprotective" levels of either PNT (5), PTB (10), or hypothermia (A. Artru and J. D. Michenfelder, unpublished data) were established over 50 minutes. In these groups either PNT, 50 mg/kg, or PTB, 33 mg/kg, was administered intravenously, or hypothermia was induced to 35 C by externally applied ice bags.

The levels chosen for each of the cerebral protective treatments in the latter three groups were considered equiprotective since they were previously reported to provide equivalent cerebral protection in the hypoxic ($F_{IO_2} = 0.05$) mouse model, yet are well below maximal protective levels wherein the toxic effects of each begin to limit the protective effects (5, 10). N_2O was included in the inspired gases of the control animals to provide some measure of central nervous system depression as occurred in the other groups due to PNT (5), PTB (10), or hypothermia (A. Artru and J. D. Michenfelder, unpublished data).

At 50 minutes, systemic values were again determined, the cisterna magna was cannulated through the previously prepared site using an 18-gauge Touhy needle, and 0.3 ml of CSF was withdrawn for control measurements of $[K^+]_{CSF}$ and $[Na^+]_{CSF}$ using an IL 143 flame photometer (Instrumentation Laboratory, Inc.). Circulatory arrest was then induced by abruptly reducing F_{IO_2} to 0, and CSF samples (0.3 ml) were again obtained via the indwelling cannula 10 and 20 minutes after arrest was achieved. The arterial pressure and wave form were monitored to aid in determining the elapsed time from onset of anoxia to circulatory arrest. Criterion for arrest was static arterial pressure less than 2 mm Hg with absence of any arterial pressure wave form. In four of the six animals from each group the EEG was monitored to determine the time from onset of anoxia to loss of EEG activity.

The data for the systemic parameters, CSF electrolytes, and time to circulatory arrest were subjected to analysis of variance. When variance was confirmed, values within each group were compared by paired *t*-test and values between groups compared by unpaired *t*-test.

Results

Control values for CSF electrolytes were similar in all six groups (Table 1). After circulatory arrest, values for $[K^+]_{CSF}$ were significantly lower at 10 and 20 minutes in the groups that received PNT, 50 and 150 mg/kg, than in the control group. At both time intervals PNT, 150 mg/kg, tended to provide a greater reduction in $[K^+]_{CSF}$ accumulation than PNT, 50 mg/kg. Hypothermia reduced $[K^+]_{CSF}$ accumulation to a lesser degree than PNT, 50 mg/kg, whereas PTB and the PNT vehicle had no effect. Loss of EEG activity was equivalently delayed in the groups that received PTB, hypothermia, and PNT, 50 mg/kg, compared to the control group, but occurred earlier in the group that received PNT, 150 mg/kg (Table 2). The time to circulatory arrest following the institution of anoxia was the same in all groups except the group that received PNT, 150 mg/kg, in which circulatory arrest occurred earlier.

The systemic values measured for each group be-

TABLE 1
CSF Electrolyte Values*

Group	Prearrest		10 min postarrest		20 min postarrest	
	K^+	Na^+	K^+	Na^+	K^+	Na^+
	meq/L					
I—N_2O control	4.4 ± 0.4	152 ± 4	10.9 ± 0.8†	149 ± 4	19.9 ± 1.3†	144 ± 7†
II—Phenytoin, 150 mg/kg	4.1 ± 0.3	150 ± 2	7.8 ± 1.0†‡	152 ± 2	12.4 ± 0.9†‡	149 ± 2
III—Vehicle for phenytoin	4.4 ± 0.4	152 ± 4	11.0 ± 1.0†	150 ± 4	19.7 ± 1.4†	145 ± 3†
IV—Phenytoin, 50 mg/kg	4.3 ± 0.5	148 ± 4	8.4 ± 0.4†‡	149 ± 3	13.8 ± 1.1†‡	148 ± 3
V—Pentobarbital, 33 mg/kg	4.1 ± 0.2	153 ± 3	10.7 ± 1.0†	151 ± 3	21.0 ± 1.6†	143 ± 2†
VI—Hypothermia, 35 C	4.4 ± 0.3	151 ± 3	9.7 ± 0.2†	148 ± 2	15.2 ± 1.2†‡	144 ± 2

* Values are means ± SEM. N = 6 for each group.
† Significantly different from prearrest, $p < 0.02$.
‡ Significantly different from control, $p < 0.05$.

TABLE 2
Postanoxia Values*

Group	Time	
	Loss of EEG	Circulatory arrest
	min	
I—N_2O control	2.2 ± 0.2	9.1 ± 0.3
II—Phenytoin, 150 mg/kg	0.9 ± 0.3†	7.2 ± 0.7†
III—Vehicle for phenytoin	2.0 ± 0.3	9.5 ± 0.4
IV—Phenytoin, 50 mg/kg	2.9 ± 0.2†	9.2 ± 0.3
V—Pentobarbital, 33 mg/kg	3.1 ± 0.1†	8.8 ± 0.4
VI—Hypothermia, 35 C	3.3 ± 0.1†	9.4 ± 0.3

* Values are means ± SEM.
† Significantly different from control, $p < 0.05$.

fore administration of PNT, the PNT vehicle, PTB, or hypothermia were not significantly different with Pa_{O_2} > 127 ± 8 mm Hg; Pa_{CO_2}, 38 to 39 mm Hg; buffer base, 42 to 47 mEq/L; Hb > 10.8 ± 0.3 g/dl; mean arterial pressure > 96 ± 6 mm Hg; and pharyngeal temperature, 38.0 to 38.3 C. Administration of the treatments produced no significant changes within or between groups except in the hypothermic and PNT, 150 mg/kg, groups. In the former group a significant reduction in temperature occurred as intended (35 C). In the latter group mean arterial pressure, though statistically reduced following infusion of PNT, remained adequate at 88 ± 3 mm Hg.

Discussion

The effect on $[K^+]_{CSF}$ accumulation observed for each of the treatments (PNT, hypothermia, PTB), as well as the N_2O controls, was similar to that reported for each individually in separate models and species (5, 6, 9). Our results were also consistent with other recent studies that employed microelectrodes to measure $[K^+]$ in the cerebral extracellular space. Heinemann and Lux (11) reported that PNT, 15 to 25 mg/kg, reduced the amplitude of the increase in extracellular $[K^+]$ during stimulation of cat cortex. By contrast, Nataf et al (12) reported that administering Nembutal before brief periods of asphyxic hypoxia increased the rise in extracellular $[K^+]$ in rat cerebral cortex.

The results of the present study support the hypothesis that the ability of PNT to reduce $[K^+]_{CSF}$ accumulation may be linked to its protective effect. At equiprotective doses, PNT caused a greater reduction in the rate of $[K^+]_{CSF}$ accumulation than the other two treatments, wherein protection is likely explained by a different mechanism (i.e., reduced cerebral metabolism). In addition, the ability of PNT to reduce $[K^+]_{CSF}$ accumulation tended to be dose-related, similar to the dose-related cerebral protective effect of PNT (1, 3, 5). The PNT vehicle had no effect on $[K^+]_{CSF}$ accumulation, suggesting that PNT itself, rather than some component of the vehicle or a change in pH, was responsible for the decreased rate of $[K^+]_{CSF}$ accumulation. In the present study this effect is likely explained by a reduction in the net outward flux of K^+ from hypoxic cells (2, 13, 14). Decreased intracellular K^+ release may result from enhanced function of the ATP-dependent Na-K pump (14–16), an energy-independent membrane stabilizing effect (17–19), or another mechanism as yet unknown.

The effect of PNT on $[K^+]_{CSF}$ accumulation was not statistically significance with respect to dose; this probably explained by the CSF sampling technique used in the present study. The degree to which sampled cisternal $[K^+]_{CSF}$ reflects intracellular K^+ release depends on several factors, such as the rate of movement of K^+ from the cerebral extracellular space to the CSF, the size of the compartment containing the CSF, the number of CSF samples taken, and the volume of CSF taken with each sample (In the rabbit

the intraventricular CSF volume is 1.6 to 2.1 ml and the turnover rate is 0.48%/min (20)). With the sampling technique we used, detection of any effect of PNT on either magnitude or rate of K^+ release would have been both delayed and blunted. Thus differences in $[K^+]_{CSF}$ with PNT, 50 mg/kg, vs 150 mg/kg might not achieve statistical significance until an interval of greater than 20 minutes had elapsed following circulatory arrest.

There are several means by which limiting cerebral $[K^+]$ accumulation could explain PNT-induced cerebral protection. A large increase in extracellular $[K^+]$ causes contraction of vascular smooth muscle (21–24). Wade et al (8) reported that during global anoxia in rats an increase in cerebrovascular resistance and decrease in cerebral perfusion rate is associated with an increase in $[K^+]_{CSF}$ above 8 to 9 meq/L. Elevated extracellular $[K^+]$ has also been reported to promote increases in astroglial water content and to cause cytotoxic edema (25). As a result, diffusion pathways for substrates and metabolites are lengthened and vascular lumens are narrowed due to compression. Finally, large increases in extracellular $[K^+]$ may be directly toxic to neural tissue (26). Thus, limiting cerebral K^+ accumulation should improve the distribution of cerebral blood flow, improve energy/substrate delivery, and prevent the accumulation of metabolites and toxic substances.

The time to onset of an isoelectric EEG was similarly delayed in animals given PNT, 50 mg/kg, PTB, and hypothermia; this supports our choice of these levels as equiprotective. For PTB and hypothermia this effect can be explained by a reduction in CMR_{O_2} that will reduce the rate of energy/substrate depletion[27]. Assuming an effect of PNT on CMR_{O_2} in the rabbit similar to that in normoxic dogs (i.e., no reduction in CMR_{O_2}), the delay in loss of EEG activity suggests that PNT permits a relatively greater depletion of energy/substrate levels before cortical electrical activity ceases. Alternatively the cerebral metabolic effects of PNT may be altered during hypoxemia so that the rate of energy/substrate depletion is reduced, similar to that seen with PTB or hypothermia.

In a previous study (5) the authors reported that PNT produced a dose-related increase in survival time in hypoxic ($F_{IO_2} = 0.05$) mice and significant circulatory depression at large doses in normoxic dogs. It was speculated that the "bell" shape of the curve, relating hypoxic survival time to PNT dose, was a result of the toxic systemic effects of PNT outweighing the beneficial effects at large doses. Similarly, in the present study the toxic systemic effects of large doses of PNT likely explains the earlier time to anoxic circulatory arrest. The earlier loss of EEG activity following anoxia likely relates to a more rapid loss of cerebral perfusion as well as the reduction in EEG frequency that accompanies large doses of PNT.

In summary, cerebral protective doses of PNT significantly reduced $[K^+]_{CSF}$ accumulation and tended to do so in a dose-related manner. PNT reduced K^+ more effectively than equiprotective levels of hypothermia or PTB whose protective effects are commonly explained by their ability to reduce CMR_{O_2}. The present data support the hypothesis that PNT-induced cerebral protection may be linked to its effect on cerebral K^+ accumulation.

REFERENCES

1. Hoff EC, Yahn C. The effect of sodium 5,5-diphenylhydantoin (dilantin sodium) upon the tolerance of rats and mice to decompression. Am J Physiol 1944;141:7–16.
2. Baldy-Moulinier M. Cerebral blood flow and membrane ionic pump. Eur Neurol 1971/72;6:107–113.
3. Naiman JG, Williams HL. Effects of diphenylhydantoin on the duration of respiratory activity during anoxia. J Pharmacol Exp Ther 1964;145:34–41.
4. Cullen JP, Aldrete JA, Jankovsky L, Romos-Salas F. Protective action of phyenytoin in cerebral ischemia. Anesth Analg 1979;58:165–169.
5. Artru AA, Michenfelder JD. Cerebral protective, metabolic and vascular effects on diphenylhydantoin. Stroke 1980;11:377–382.
6. Bering EA. Effects of profound hypothermia and circulatory arrest on cerebral oxygen metabolism and cerebrospinal fluid electrolyte composition in dogs. J. Neurosurg 1974;40:199–205.
7. Meyer JS, Kanda T, Sinohara Y, Fukuuchi Y. Effects of anoxia on cerebrospinal fluid sodium and potassium concentrations. Neurology 1971;21:869–895.
8. Wade JG, Amtrop O, Sorensen SC. No-flow state following cerebral ischemia. Arch Neurol 1975;32:381–384.
9. Wade JF, Sorensen SC. Effect of anaesthetic agents on the ionic composition of cerebrospinal fluid following total cerebral ischaemia. Can Anaesth Soc J 1978;25:22–24.
10. Steen PA, Michenfelder JD. Barbiturate protection in tolerant and non-tolerant hypoxic mice: comparison to hypothermic protection. Anesthesiology 1979;50:404–408.
11. Heineman V, Lux HD. Effects of diphenylhydantoin on extracellular (K^+) in cat cortex. Electroencephalogr Clin Neurophysiol 1973;34:735.
12. Nataf N, Gourmel G, Rossignol P. Pharmacological actions on hypoxia increase of cortical extracellular K^+ ion: doesn't it explain cerebrovascular effects of some drugs in hypoxia? Acta Neurol 1977;56:366–367.
13. Pincus JH, Grove I, Marino BB. Studies on the mechanism of action of diphenylhydantoin. Arch Neurol 1970;22:566–571.
14. Escueta AV, Appel SH. Brain synapses: an in vitro model for the study of seizures. Arch Intern Med 1972;129:333–344.
15. Fertziger AP, Liuzzi SE, Dunham PB. Diphenylhydantoin: stimulation of potassium influx in lobster axons. Brain Res 1971;33: 592–596.
16. Festoff BW, Appel SH. Effect of diphenylhydantoin on synaptosome sodium-potassium-ATPase. J Clin Invest 1968;47: 2752–2758.
17. Crane P, Swanson P. Diphenylhydantoin and the cations and phosphates of electrically stimulated brain slices. Neurology 1970;20:1119–1123.

18. Nasello AG, Montini EE, Astrada CA. Effects of veratrine, tetraethylammonium, and diphenylhydantoin on potassium release by rat hippocampus. Pharmacology 1972;7:89–95.
19. Pincus JH. Diphenylhydantoin and ion flux in lobster nerve. Arch Neurol 1972;26:4–10.
20. Pollay M, Davson H. The passage of certain substances out of the cerebrospinal fluid. Brain 1963;86:137–150.
21. Keatinge WR. Electrical and mechanical responses of vascular smooth muscle in vasodilator agents and vasoactive polypeptides. Circ Res 1966;18:641–643.
22. Konold P, Gebert G, Brecht K. The effect of potassium on the tone of isolated arteries. Pfluegers Arch 1968;301:283–291.
23. Freeman DJ, Daniel EE. Calcium movement in vascular smooth muscle and its detection using lanthunum as a tool. Can J Physiol Pharmacol 1974;51:900–913.
24. Halloway ET, Bohr DF. Reactivity of vascular smooth muscle in hypertensive rats. Circ Res 1973;33:678–685.
25. Bourke RS, Kimelberg HK, Dazé MA, Popp AJ. Studies on the formation of astroglial swelling and its inhibition by clinically useful agents. In: Neural trauma. New York: Raven Press, 1979: 95–113.
26. Hilarowicz H, Szajua M. Über den Einfluss der subduralen Darreichung von Kaliumchlorid auf die Vasomotoren-, Herzhemmungs-und Atemzentren. Ziges Exp Med 1929;64:772–786.
27. Michenfelder JD, Theye RA. Cerebral protection by thiopental during hypoxia. Anesthesiology 1973;39:510–517.

Brachial Plexus Injury following Median Sternotomy

Brachial plexus injuries are frequently present after median sternotomies and vary from those causing minor symptoms to those producing major disability. In two groups of patients operated upon with the arms either abducted to a 90-degree angle or at the sides there was no difference in the incidence of brachial plexus injury. However, the finding of Horner's syndrome in one patient and the finding in another (at autopsy) of brachial plexus penetration by a fractured first rib suggested that traction on the brachial plexus was not the correct pathogenesis of the injury. A concomitant autopsy study demonstrated fractured first ribs penetrating the brachial plexus in 11 of 15 patients whose sternum was opened with the sternal retractor placed in the usual location, but in none of 15 patients whose sternum was opened with the retractor placed two intercostal spaces caudally. The injury can be minimized by opening the sternal retractor as little as is necessary and by placing it as caudally as possible commensurate with adequate exposure. *(Vander Salm TJ, Cereda JM, Cutler BS: Brachial plexus injury following median sternotomy. J Thorac Cardiovasc Surg 1980;80:447–452)*

New Developments in Cardiopulmonary Resuscitation

The traditional concept of cardiopulmonary resuscitation (CPR) is that the heart is squeezed between the sternum and the spine during external cardiac massage to create a pressure gradient that forces blood from the heart to the periphery. Although the heart may actually be squeezed in some persons by this maneuver, a newer view of CPR holds that closed-chest compression produces a generalized rise in intrathoracic pressure that is applied to the pulmonary vascular bed as well as the heart. Thus, the heart does not serve primarily as a pump during external cardiac massage but instead acts as a conduit for blood from the lungs. Furthermore, flow into extrathoracic vessels depends on their tendency to remain open or to collapse: forward flow occurs across the head during CPR because a pressure gradient is developed between the carotid artery and the more compressible jugular vein. These concepts have important clinical implications and greatly increase the understanding of the physiology of CPR. *(Luce JM, Cary JM, Ross BK, Culver BH, Butler J: New developments in cardiopulmonary resuscitation. JAMA 1980;244:1366–1370)*

REVIEW article

Postoperative Recovery of Pulmonary Function

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THE POSTOPERATIVE period is frequently associated with clinically important abnormalities of pulmonary function. Following surgery of the abdominal or thoracic cavities, postoperative changes are invariable and severe with recovery of function delayed for days or weeks. This review summarizes the current knowledge about postoperative pulmonary function, emphasizing recent improvements in the understanding of the etiology of postoperative abnormalities, their prevention, and their treatment.

Awareness of postoperative pulmonary dysfunction as a major problem is longstanding. Pasteur (1), in 1910, described lobar collapse of the lung after abdominal operations. His speculation about the etiology of the collapse has proved prophetic: "I feel sure that when the true history of postoperative lung complications comes to be written, active collapse of the lung, from deficiency of inspiratory power, will be found to occupy an important position among determining causes." The role of shallow breathing, without periodic "sighs" in producing hypoxemia ("anoxemia") was identified by Haldane et al (2), in 1919. Beecher's 1932 classic report (3) of reduced lung volumes after laparotomy signaled the start of attempts to quantitate mechanical lung function changes following surgery. Beecher correctly identified the functional residual capacity (FRC) ("subtidal volume") as "the most significant of all lung volumes (3)." The appropriateness of this designation has become more apparent only recently.

A major emphasis of this review will be the development of the argument in favor of the reduced FRC as the single most important mechanical abnormality. The observed changes in pulmonary mechanics in the postoperative period will be viewed as the primary changes, with gas exchange abnormalities secondary. Postoperative changes in respiratory control will be seen as a third interacting factor. Finally, treatment designed to limit the extent of postoperative pulmonary function changes, or to speed recovery, will be discussed.

The information reviewed in examining mechanical factors, gas exchange, and respiratory control in the postoperative period relates to patients with normal pulmonary function before surgery. The important problem of the patient with preexisting pulmonary abnormalities, with respect to preoperative assessment (4) and preparation (5), and management during the intraoperative and postoperative periods (6), is beyond the scope of this review. Similarly, pulmonary defense mechanisms (7) have not been included.

Mechanical Factors

The characteristic postoperative mechanical respiratory abnormality following abdominal or thoracic surgery is a restrictive pattern with severely reduced inspiratory capacity and vital capacity (VC) plus smaller, but more important, reductions in FRC (8–10). Patients breathe rapidly with a small tidal volume and are unwilling or unable to inspire deeply. The reduced inspiratory capacity limits the patient's ability to cough effectively.

Figs 1 and 2 summarize the clinically important lung volume changes following upper and lower ab-

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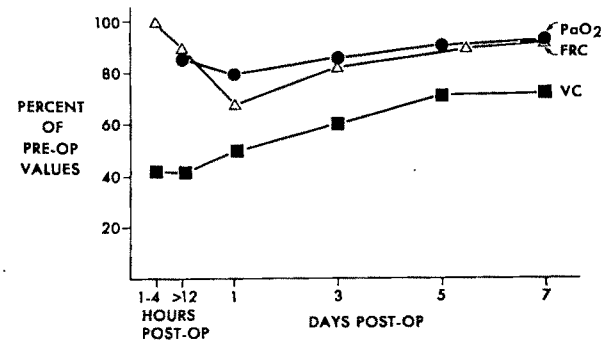


FIG 1. Postoperative VC, FRC, and Pa_{O_2} (FI_{O_2}.21) (as percent of preoperative values) following upper abdominal surgery (references 8–10, 29, and D. H. Reimer, M. B. Burnham, D. B. Craig, unpublished observations.)

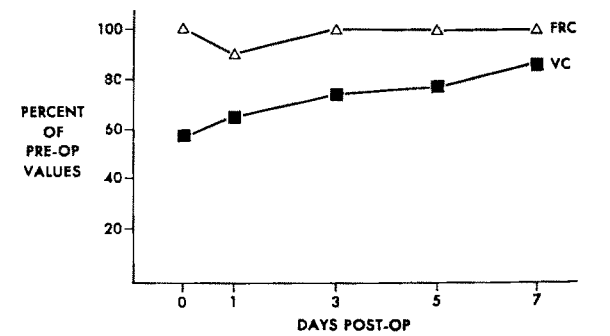


FIG 2. Postoperative VC and FRC (as percent of preoperative values) following lower abdominal surgery (references 8–10, and D. H. Reimer, M. B. Burnham, D. B. Craig, unpublished observations.)

dominal surgery. Immediately following upper abdominal surgery, VC is normally reduced to approximately 40% of preoperative values and remains depressed, but less so, for at least 10 to 14 days. Unfortunately most studies have ended at 5 to 7 days at which time VC is still only 60% to 70% of preoperative levels. Information is lacking to demonstrate when full recovery of VC occurs after upper abdominal surgery.

Markedly lesser changes in VC are noted after surgery of the lower abdominal cavity (8, 10). Superficial or extremity surgery is not associated with any ongoing abnormality of lung volumes (8, 10). In view of the absence of changes in this latter category of patients, it is possible to conclude that the anesthetic administered is not in itself a primary factor producing ongoing postoperative pulmonary mechanical abnormalities. This conclusion is important because it suggests that the primary etiology of the mechanical changes of the respiratory system during general anesthesia (11) and after surgery are not the same. However, it is likely that the anesthetic may be a contributing factor to postoperative pulmonary dysfunction, particularly in patients at increased risk of respiratory complications (12).

It has been known for decades that FRC is reduced following certain types of surgery. This reduction is now appreciated as being the most clinically important lung volume change because of its functional consequences (10), which will be discussed later. As Fig 1 summarizes, by 24 hours following upper abdominal surgery, FRC decreases to about 70% of preoperative levels, remains depressed for several days, then gradually returns to normal by day 7 to 10. It had long been assumed that FRC was already decreased at the termination of surgery. However, measurements at 4, 10, and 16 hours following cholecystectomy failed to demonstrate a significant decrease in FRC until 16 hours (8).

In another study (13), in which only single FRC measurements were made at 1 to 4 hours following upper abdominal surgery, FRC was unchanged from preoperative levels. This finding has important implications. First, it suggests, as does the other information outlined above, that the etiology of the general anesthesia-induced changes in FRC is different from the etiology of postoperative changes. Second, the delay in development of a reduced FRC suggests the possibility of therapeutic interventions that will limit the FRC changes. Fig 2 demonstrates the lesser fall and more rapid recovery of FRC following lower abdominal surgery. FRC is unchanged following superficial (8) or extremity surgery (10).

The importance of the reduced FRC has become apparent through the understanding of the phenomenon of small airway closure (14, 15). The small airways (less than 1.0 mm diameter) in the periphery of the lung are not supported by cartilage and so are influenced by transmitted pleural pressures. Normally pleural pressures are less than atmospheric, producing a positive transpulmonary pressure which distends the lung, including the small airways. If one breathes at a reduced FRC, either voluntarily due to effort or involuntarily due to, for example, abdominal pain, higher than atmospheric pleural pressures will exist in gravity-dependent areas of the lung. Pleural pressure greater than atmospheric pressure results in a negative transpulmonary pressure causing small airways to be narrowed or closed. Whether small airways are narrowed or closed, the net result is reduction in ventilation to affected lung regions, producing low ventilation/perfusion ($\dot{V}/\dot{Q}$) relationships, thereby impairing gas exchange and leading to hypoxemia. Furthermore, failure of an airway to reopen

will, in time, lead to total collapse of the lung unit served by the airway, producing the clinical syndrome of atelectasis. If an absorbable gas (for example, N_2O or O_2) is trapped behind the closed airway, atelectasis will occur more rapidly (16).

The lung volume at which small airway closure is thought to begin to occur is the closing capacity (CC) (the lung volume at which gravity-dependent lung regions cease to ventilate, presumably due to small airway closure). When the CC exceeds FRC (Fig 3), regions with low $\dot{V}/\dot{Q}$ ratios develop, leading to impaired gas exchange and possibly to gas trapping and atelectasis. Airway closure above FRC can be present due to breathing at reduced lung volumes as discussed above or due to an increased degree of airway closure because of age, pulmonary disease, cigarette smoking, or pulmonary edema (14, 15) (Fig 3). It must be emphasized that although it is the overall FRC and CC for the two lungs that are measured and compared, it is, of course, the regional degree of airway closure and the regional FRC that are important.

The lack of change in the forced expired volume in 1 second, as a fraction of the total forced vital capacity (FEV_1/FVC) has been interpreted as indicating an absence of large airway obstruction following upper abdominal surgery (17). It is likely, however, that more specific tests of airway resistance would demonstrate an increased resistance in the presence of a decreased FRC, which would be expected to reduce airway caliber.

Gas Exchange

Gas exchange abnormalities in the postoperative period have two temporal patterns (18). First is the arterial hypoxemia that occurs immediately following anesthesia and surgery, lasting from several minutes to approximately 2 hours. Causes of the early postoperative hypoxemia are related to the preceding general anesthetic rather than to the ongoing pulmonary mechanical factors described above. Alveolar hypoventilation, $\dot{V}/\dot{Q}$ mismatch, right to left shunting of blood, depressed cardiac output, and increased oxygen consumption due to hypertonic muscles and shivering are potential causative factors (18). Additional factors specific to this time period include diffusion hypoxia produced by the change from a gas mixture containing nitrous oxide to one containing nitrogen, and hypoxemia produced by hypoventilation due to depletion of carbon dioxide stores during preceding hyperventilation (18). Impairment of the compensatory mechanism of hypoxic pulmonary vasoconstriction by anesthetic agents (19), will exaggerate the hypoxemia-producing effects of low $\dot{V}/\dot{Q}$ areas in the lung.

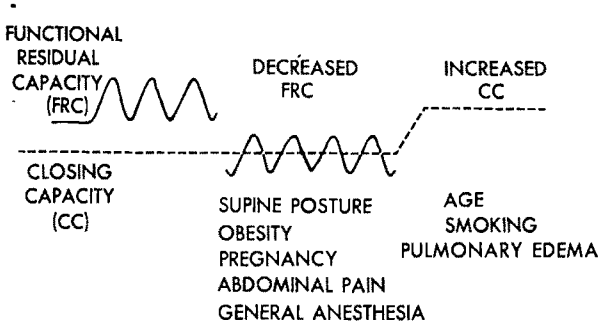


FIG 3. Relationship of CC to FRC. In young healthy patients FRC normally is larger than CC (left). If FRC falls (middle), or CC rises (right), small airway closure may occur during normal breathing. See text for details.

Normally, in the absence of preexisting abnormalities of pulmonary function, return of gas exchange to normal following uncomplicated general anesthesia for minor operations occurs within the first 2 hours following surgery. The second pattern, ongoing gas exchange abnormalities, are, for the most part, associated with surgical procedures that either affect the patient's ability to inspire deeply or that cause the patient to be immobilized in bed. The maximum defect in gas exchange is seen following surgery of the thorax or upper abdomen. The characteristic defect is arterial hypoxemia, without hypercarbia (18).

The best correlations of the degree of postoperative hypoxemia are with reductions in FRC (8, 10) and with the relationship of the CC to FRC (10). Fig 1 summarizes the time course of postoperative hypoxemia, following upper abdominal surgery. Full return to preoperative levels does not occur until approximately 2 weeks following surgery (20). Age, more than site of operation (upper abdomen, lower abdomen, superficial), has been shown to relate to the degree of reduction in postoperative P_{O_2} (21). Once the postoperative gas exchange defect becomes established, the abnormalities observed are $\dot{V}/\dot{Q}$ mismatch and right to left shunting of blood (21, 22).

In addition to the mechanisms of small airway closure, gas trapping, and atelectasis discussed above, other factors that produce arterial hypoxemia may also be present. These include ventilation maldistribution due to the abnormal pattern of breathing (rapid frequency, small tidal volume) or other causes, increased flow of mixed venous blood through "anatomic shunts," and a reduction in the mixed venous oxygen content due to increased oxygen consumption, reduced cardiac output, or reduced oxygen carrying capacity.

Respiratory Control

As with gas exchange, postoperative abnormalities of respiratory control are best considered in two phases. The early phase is due to the presence of agents used during the anesthetic, then followed by effects of narcotic analgesics used in the later postoperative period.

Respiratory depression is a well known effect of inhalational anesthetic agents. Not only do volatile anesthetics cause alveolar hypoventilation and reduce the response to carbon dioxide, but they also severely blunt the ventilatory response to hypoxemia (23, 24). Of special importance is the reduced response to hypoxemia by 0.1 minimum alveolar concentration (MAC) enflurane (23) or halothane (24). These subanesthetic doses also reduce by more than half the ventilatory response to acidemia (25). These studies identify an additional important factor active in the immediate postoperative period. At a time when hypoxemia is very likely to occur, the normal response of an increase in ventilation may not occur or may be reduced.

What effects do narcotic analgesics have on respiratory control? We know that narcotics depress alveolar ventilation, leading to small increases in arterial P_{CO_2} (26, 27). In addition, the pattern of breathing can be altered, with elimination of the periodic sighs that are important in maintaining lung inflation. Further, small doses of morphine (7.5 mg subcutaneously) depress both the hypoxic and the hypercapnic ventilatory drive (26). Narcotic analgesics then, whether present as a residual from the intraoperative period (28), or administered remotely, have effects that are in part undesirable, and that may promote continuation or worsening of the basic mechanical pulmonary abnormalities discussed above.

Prevention and Treatment

Can the restrictive pulmonary pattern and accompanying hypoxemia following abdominal surgery be prevented? The literature suggests that these changes can be modified, but not prevented. The key therapeutic goal appears to be maintenance or restoration of FRC. Although this section will emphasize the effects of treatment on lung volumes, some information will be reviewed that suggests that this maintenance of lung volumes will have favorable effects on gas exchange.

There is incomplete understanding of the mechanisms producing the restrictive pattern. Although pain and muscle splinting in response to pain are assumed by most to be the principal causative factors, total relief of pain following upper abdominal surgery, using epidural analgesia resulted in only partial restoration of VC, while FRC was only minimally changed (29) (Fig 4). Thoracic epidural analgesia alone, in the absence of pain, did not change VC or FRC (30). Even in the absence of pain, when epidural analgesia was administered from the time of the patient's awakening from anesthesia, reductions in VC still developed following upper abdominal surgery (31). It must be concluded that other factors, in addition to pain, are active. The incision and necessary trauma of the surgical procedure must interfere with the function of the "chest wall," of which the diaphragm and adjacent abdominal contents and abdominal wall are essential components. Pain and the chest wall lesion would reduce VC. With shallow and monotonous breathing, without the normal periodic sigh, instability of peripheral lung units results, leading to alveolar collapse. In those patients in whom, in addition, small airway closure is occurring during tidal breathing, a further factor promoting alveolar collapse is present, as has been outlined above.

There is limited evidence to suggest that the specific surgical approach and the type of incision influences postoperative pulmonary function. In patients undergoing esophageal resection, a two-incision laparatomy and thoracotomy affected pulmonary function less than a single incision thoracolaparotomy (32). Following cholecystectomy, patients with a subcostal incision had less depression of VC, less hypoxemia, and a lower incidence of postoperative pulmonary complications than patients who received a midline incision (33).

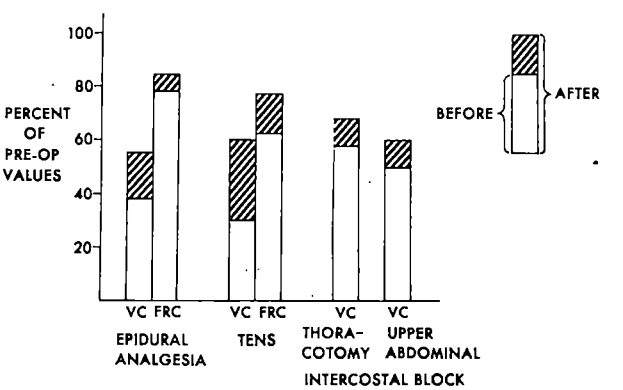


FIG 4. Results of treatment of postoperative pain on VC and FRC. Open portions of bars indicate either pretreatment values or values in untreated control group. Cross-hatched portions indicate results with treatment. Source of information and time of study: epidural, Wahba (29), combination of day 0 and day 1; transcutaneous electrical nerve stimulation (TENS), Ali et al (45), day 0; intercostal block, thoracotomy, Toledo-Pereyra and DeMeester (43), day 3, upper abdominal surgery, Engberg (41), day 0.

Since total prevention of the restrictive pulmonary abnormality following upper abdominal surgery is not possible, attention has appropriately been focused on therapy that modifies either the severity or the functional consequences of the respiratory changes. The large number of therapeutic approaches described suggests that no single method has been widely accepted as superior.

Techniques or devices that either encourage or force the patient to inspire deeply are of the most clinical importance (34–36). The aim is to produce a large and sustained increase in transpulmonary pressure, distending the lung. If the positive transpulmonary pressure is large enough and for a sufficient duration, collapsed lung units will reexpand. The only practical way to monitor the adequacy of inspiratory maneuvers is to measure the actual volume inspired. There is evidence that "stir up" programs that include voluntary deep breathing are either superior to (34, 35), or equal in benefit to (37), episodic use of intermittent positive-pressure breathing. Intermittent positive-pressure breathing may be of special benefit in the occasional patient, but it has not been shown to be superior to other approaches in the general population of postoperative patients, and, as noted, may in some circumstances be inferior. Older techniques such as "blow bottles" are now recognized as deflationary, and do not produce the desired maintenance of lung inflation (35). They should be abandoned. Any maneuver that causes the patient to expire below FRC is undesirable. This would include the measurement of VC, which involves exhalation to residual volume.

The beneficial effect on gas exchange of a simple posture change from supine to seated has been demonstrated, both in normal subjects (38) and following upper abdominal surgery (39). The improvement in gas exchange in the seated posture is thought to be due to the observed increase in FRC, without a change in the CC (38). Distribution of ventilation, and gas exchange, improve.

Pain relief using narcotic analgesics has been shown to be inferior, with respect to limiting pulmonary complications, to epidural analgesia (31, 40) or to unilateral intercostal blockade (41). Narcotics should not be viewed as a complete therapeutic modality themselves, but only as a method of partial pain relief allowing other components of therapy, including stir up programs to be better accepted by the patient and more effective.

The role of intercostal nerve blocks is controversial. Although some feel that intercostal nerve block for relief of postoperative pain of the thorax or upper abdomen is the technique of choice (42), it has been suggested that bilateral blockade of a large number of intercostal nerves may adversely affect some patients' ability to cough, and so lead to the retention of secretions (41). An effective approach to the limitation of VC changes following thoracotomy is the direct intrathoracic block of intercostal nerves at the conclusion of surgery (43) (Fig 4).

Epidural analgesia following upper abdominal surgery, as noted above, partially restored VC, but FRC remained unchanged (30). In a separate study in which FRC was not measured, epidural analgesia was associated with better oxygenation than was the use of morphine (31). Although FRC and gas exchange data in the same group of patients is not available, the results of these separate studies emphasize that the reduced FRC must be but one of many factors. There is concern that postoperative use of epidural analgesia may be an unnecessarily complex solution to the problem for the average patient. Most would reserve its use for the occasional patient at increased respiratory risk. Epidural narcotic administration has been shown to relieve postoperative pain and to partially restore pulmonary function FEV_1 (44). There is, however, a serious potential risk of associated respiratory depression.

The pulmonary function sparing effect of transcutaneous electrical nerve stimulation (TENS) following cholecystectomy (45) has been reported (Fig 4). This technique, although requiring special instrumentation, is attractive in its simplicity and effectiveness. Postoperative VC in treated patients was approximately 60% of preoperative values, compared to approximately 40% in a control group. FRC was approximately 80% and 60%, respectively. Remarkably, postoperative Pa_{O_2} was unchanged from preoperative values in the group which received TENS. This partial preservation of FRC and the absence of postoperative changes in Pa_{O_2} suggests that the use of TENS should be investigated further.

Psychological factors influencing postoperative pain, and the patient's response to pain, must be recognized (46). Preoperative patient instruction and reassurance has been shown to reduce the amount of narcotic analgesics employed (46). Other methods of postoperative pain therapy shown to be of some benefit include inhalation of low concentrations of nitrous oxide or volatile anesthetic agents and hypnosis and acupuncture (46); however, enthusiasm for these techniques has been limited.

Therapy that maintains or improves lung inflation,

as discussed above, is also associated with improvement in oxygenation. Oxygenation was better in patients who received epidural analgesia for pain relief than in patients who received morphine (31). In specific circumstances, intercostal nerve blocks (41) and TENS (45) have improved oxygenation during at least part of the postoperative course. Regardless of the method employed, as lung inflation is improved oxygenation can be expected to improve.

Discussion and Summary

Postoperative abnormalities of mechanical pulmonary function and of gas exchange after surgery involving the abdominal or thoracic cavities should be recognized as the rule rather than the exception. The early postoperative phase (within the first 2 hours) characterized by arterial hypoxemia, with or without alveolar hypoventilation, is followed by a second delayed phase in which mechanical abnormalities dominate with accompanying arterial hypoxemia. During both phases, respiratory control may be impaired such that the normal respiratory response to arterial hypoxemia, hypercarbia, or acidemia is blunted or absent.

The early postoperative hypoxemia appears clearly to be a continuation of the hypoxemia associated with general anesthesia, with the possible additional factors of diffusion hypoxia and posthyperventilation hypoventilation. The immediate reduction in VC and the delayed decrease in FRC (18 to 24 hours) following abdominal surgery are the important mechanical abnormalities. The time for full recovery of VC to preoperative values is unknown, but appears to be in excess of 3 weeks. FRC returns to normal within 2 weeks.

In spite of the frequency and importance of postoperative pulmonary mechanical abnormalities, the published information is almost exclusively a quantitation of the end results. Missing are examinations of possible mechanisms producing the observed restrictive pattern. It appears that pain, plus a lesion of the chest wall due to the incision, and the localized trauma of the surgical procedure lead to the reduced VC. Since complete pain relief neither prevents the loss of VC nor fully restores it once lost, pain must be but one of several active factors. The chest wall lesion, plus the effects of rapid shallow breathing, without periodic sighs, lead to the fall in FRC. Small airway closure with trapping of gas beyond closed airways will, in some patients, be an additional mechanism leading to loss of lung volume and a further reduced FRC. Secondary to the limited VC (or more specifically inspiratory capacity), impairment of the cough mechanism occurs. This in turn leads to retention of secretions, producing airway obstruction or a focus for infection.

The mechanisms of gas exchange abnormalities, although not proven, relate best to the reduced FRC, and the relationship of FRC to the closing capacity. Breathing at low lung volumes leads to an increased frequency of low $\dot{V}/\dot{Q}$ ratios and to enlargement of the right to left shunts.

Identification of FRC as the single most important lung volume in the postoperative patient provides a specific goal for therapy. Any technique that maintains or improves FRC can be expected to be beneficial. Since total prevention does not seem to be possible, an appropriate objective of treatment is to limit the extent of the pulmonary function abnormalities. Effective pain relief, without respiratory depression, is the ideal. VC and FRC are partially restored and gas exchange improved.

Although there is a large gap between what is possible and what is practical, the postoperative period can be made more comfortable and less hazardous by appropriate application of a variety of methods of treatment.

REFERENCES

1. Pasteur W. Active lobar collapse of the lung after abdominal operations: a contribution to the study of postoperative lung complications. Lancet 1910;2:1080–1083.
2. Haldane JS, Meakins JL, Priestley JG. The effect of shallow breathing. J Physiol 1919;52:433–453.
3. Beecher HK. Effect of laparotomy on lung volume: demonstration of a new type of pulmonary collapse. J Clin Invest 1932;12: 651–658.
4. Tisi FM. Preoperative evaluation of pulmonary function. Am Rev Respir Dis 1979;119:293–310.
5. Gracey DR, Divertie MB, Didier EP. Preoperative pulmonary preparation of patients with chronic obstructive pulmonary disease. Chest 1979;76:123–129.
6. Heironimus TW, III. The anesthetic management of the pulmonary cripple. In: American Society of Anesthesiologists and American College of Anesthesiology. Regional refresher courses in anesthesiology. New York: JB Lippincott, Co, vol 3, 1975;89–102.
7. Brain JD. Anesthesia and respiratory defense mechanisms. Int Anesthesiol Clin 1977;15:169–198.
8. Ali J, Weisel RD, Layug AB, Kripke BJ, Hechtman HB. Consequences of post-operative alterations in respiratory mechanics. Am J Surg 1974;128:376–382.
9. Meyers JR, Lembeck L, O'Kane H, Baue AE. Changes in functional residual capacity of the lung after operation. Arch Surg 1975;110:576–582.
10. Alexander JI, Spence AA, Parikh RK, Stuart B. The role of airway closure in postoperative hypoxemia. Br J Anaesth 1973;5:34–40.
11. Rehder K. Anesthesia and the respiratory system. Can Anaesth Soc J 1979;26:451–462.

12. Hedley-White J, Burgess GE III, Feeley TW, Miller MG. Applied physiology of respiratory care. Boston: Little, Brown and Co, 1976:119–132.
13. Colgan FJ, Mahoney PD. The effect of major surgery on cardiac output and shunting. Anesthesiology 1969;31:213–221.
14. Rehder K, Marsh HM, Rodarte JR, Hyatt RE. Airway closure. Anesthesiology 1977;47:40–52.
15. Anthonisen NR. Closing volume. In: West JB, ed. Regional differences in the lung. New York: Academic Press, 1977:451–482.
16. Nunn JF. Applied respiratory physiology. 2nd ed. London: Butterworths, 1977:292–295.
17. Cheney FW. Effects of surgery on pulmonary function. In: American Society of Anesthesiologists and American College of Anesthesiology. Refresher courses in anesthesiology. New York: JB Lippincott, Co, vol 6, 1978;31–42.
18. Marshall BE, Wyche MQ Jr. Hypoxemia during and after anesthesia. Anesthesiology 1972;37:178–209.
19. Mathers JM, Benumof JL, Wahrenbrock EA. General anesthetics and regional hypoxic pulmonary vasoconstriction. Anesthesiology 1977;46:111–114.
20. Knudsen J. Duration of hypoxemia after uncomplicated upper abdominal and thoraco-abdominal operations. Anaesthsia 1970;25:372–377.
21. Kitamura H, Sawa T, Kezono E. Postoperative hypoxemia: the contribution of age to the maldistribution of ventilation. Anesthesiology 1972;36:244–252.
22. Siler JN, Rosenberg H, Mull TD, Kaplan JA, Bardin H, Marshall BE. Hypoxemia after upper abdominal surgery: comparison of venous admixture and ventilation/perfusion inequality components, using a digital computer. Ann Surg 1974;179:149–155.
23. Knill RL, Manninen PH, Clement JL. Ventilation and chemoreflexes during enflurane sedation and anaesthesia in man. Can Anaesth Soc J 1979;26:353–360.
24. Knill RL, Gelb AW. Ventilatory responses to hypoxia and hypercapnia during halothane sedation and anesthesia in man. Anesthesiology 1978;49:244–251.
25. Knill RL, Chung D, Baskerville J. Ventilatory responses to acute "Iso-PCO_2" acidosis in awake and anesthetized man (abstract). Clin Res 1978;26:879A.
26. Weil JV, McCullough RE, Kline JS, et al. Diminished ventilatory response to hypoxia and hypercapnia after morphine in normal man. N Engl J Med 1975;292:1103–1106.
27. Kafer ER, Marsh HM. The effect of anesthetic drugs and disease on the chemical regulation of ventilation. Int Anesthesiol Clin 1977;15:1–38.
28. Vejlsted H, Hansen M, Jacobsen E. Postoperative ventilatory response to carbon dioxide following neurolept anesthesia. Acta Anaesthesiol Scand 1977;21:529–533.
29. Wahba WM, Don HF, Craig DB. Post-operative epidural analgesia: effects on lung volumes. Can Anaesth Soc J 1975;22:519–527.
30. Wahba WM, Craig DB, Don HF, Becklake MR. The cardiorespiratory effects of thoracic epidural anesthesia. Can Anaesth Soc J 1972;19:8–19.
31. Spence AA, Smith G. Postoperative analgesia and lung function: a comparison of morphine with extradural block. Br J Anaesth 1971;43:144–148.
32. Black J, Kalloor GJ, Collis JL. The effect of the surgical approach on respiratory function after esophageal resection. Br J Surg 1977;64:624–627.
33. Ali J, Khan TA. The comparative effects of muscle transection and median upper abdominal incisions on postoperative pulmonary function. Surg Gynecol Obstet 1979;148:863–866.
34. Dohi S, Gold MI. Comparison of two methods of postoperative respiratory care. Chest 1978;73:592–595.
35. Bartlett RH, Bazzaniga AB, Geraghty TR. Respiratory maneuvers to prevent postoperative pulmonary complications. JAMA 1973;224:1017–1021.
36. Hedstrand U, Liw M, Rooth G, et al. Effect of respiratory physical therapy on arterial oxygen tension. Acta Anaesthesiol Scand 1978;22:349–352.
37. Ali J. The effects of intermittent positive pressure breathing (IPPB) on postoperative pulmonary function (Abstract). Ann R Coll Phys Surg Can 1979;12:36.
38. Craig DB, Wahba WM, Don HF, Couture JG, Becklake MR. "Closing volume" and its relationship to gas exchange in seated and supine positions. J Appl Physiol 1971;31:717–721.
39. Vaughan RW, Wise L. Postoperative arterial blood gas measurement: effect of position on gas exchange. Ann Surg 1975;183:705–709.
40. Modig J. Lumbar epidural nerve blockade versus perenteral analgesics. Acta Anaesthesiol Scand [Suppl] 1978;70:30–35.
41. Engberg G. Relief of postoperative pain with intercostal blockade compared with the use of narcotic drugs. Acta Anaesthesiol Scand [Suppl] 1978;70:36–38.
42. Moore DC. Intercostal nerve block for postoperative somatic pain following surgery of thorax and upper abdomen. Br J Anaesth 1975;47:284–288.
43. Toledo-Pereyra LH, DeMeester TR. Prospective randomized evaluation of intrathoracic intercostal nerve block with bupivicaine on postoperative ventilatory function. Ann Thorac Surg 1979;27:203–205.
44. Bromage PR, Camporesi E, Chestnut D. Epidural narcotics for postoperative analgesia. Anesth Analg 1980;59:473–480.
45. Ali J, Yaffe C, Serrette C. The effect of transcutaneous electric nerve stimulation on postoperative pain and pulmonary function Surgery, in press 1981.
46. Wallace PGM, Norris W. The management of postoperative pain. Br J Anaesth 1975;47:113–120.

CLINICAL reports

Evaluation of Oxygen Monitors for Use during Anesthesia

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The purpose of this study was to measure the stability and accuracy of commercial oxygen monitors that are intended for use during anesthesia. Of special interest were the effects of 3% halothane, 100% humidity, and nitrous oxide on sensor performance.

Methods

Five oxygen cells were obtained from each of four companies that market oxygen analyzers for use during anesthesia. The sensors tested were: Beckman model OM 10 (Beckman Instruments, Inc, Palo Alto, CA); Critikon model 800-021 (Critikon, Irvine, CA); IL model 402 (Instrumentation Laboratory, Andover, MA); and Teledyne microfuel cell class C-1 (Harris-Lake, Inc, Cleveland, OH). Five separate sensors from each of these four manufacturers were used making a total of 20 sensors.

The testing apparatus included two manifolds as shown in the Figure. Both manifolds had four slots to hold one sensor from each of the four manufacturers. Manifold A was used for initial calibration and for rechecking calibrations. Manifold B was used to place the sensors in the test gas—halothane, humidity, or N_2O. Three temperature probes (YSI Tele-thermometer model 43TA, Yellow Springs Instrument Co, Yellow Springs, OH) were placed in manifold B as shown in the Figure.

At the beginning of each test four of the oxygen sensors, one from each manufacturer, were calibrated in manifold A using 100% N_2 and 100% O_2, at flow rates of 5 L/min. Five minutes were allowed for complete settling before adjusting the recorder zero while in 100% N_2 and adjusting the gain while in 100% O_2. Each oxygen monitor output was recorded continuously using a Linear Instrument Corp (Irvine, CA) slow-speed strip chart recorder and all data points were taken from the chart recordings. After operating for 1 hour in room air, the oxygen sensors were recalibrated with 100% N_2 and 100% O_2 by resetting the zero and gain adjustments. The sensors were then moved to manifold B and one of the gas mixtures was introduced into the sensor manifold. On the 1st day, room air (5 L/min flow) was used. This served to measure sensor stability without introducing any interfering gases. On the 2nd day, 3% halothane in air (5 L/min) was used. The actual percent of halothane delivered by the vaporizer was verified using a Beckman LB-2 infrared gas analyzer. On the 3rd day humid air was used; 100% relative humidity was generated by passing air (5 L/min) through an Aquamid (Respiratory Care, Inc. Arlington Heights, IL) humidifier and directly into manifold B. Humidifier temperature was adjusted to maintain a mean temperature of 34 C within manifold B.

Each gas mixture passed through manifold B for 6 hours. At 2-hour intervals the sensors were physically moved from their slot in manifold B to manifold A. The sensor output was then measured after the sensors had been in dry 100% N_2, 100% O_2, and air (5 L/min flows) for 5 minutes. Sensor response time was recorded when the step change was made from 100% N_2 to 100% O_2. The time constant was defined as the

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Received from the Department of Anesthesiology, University of Utah College of Medicine, University of Utah Medical Center, 50 North Medical Drive, Salt Lake City, Utah 84132. Accepted for publication September 20, 1980. Presented in part at the International Workshop on Biomedical Transducers and Measurements, November 1978, Madrid, Spain.
Reprint requests to Dr. Westenskow.

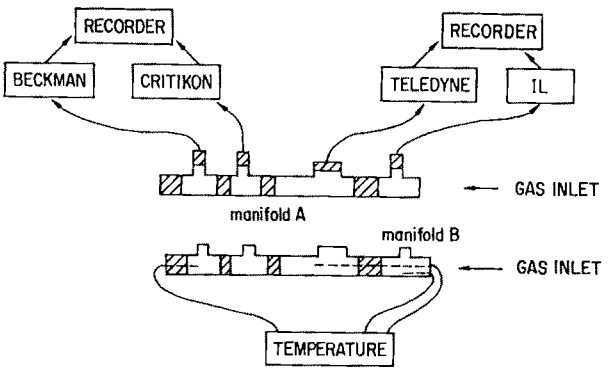


FIGURE. Dual manifold system used to evaluate the performance of four brands of oxygen monitors. Initially manifold A was used to calibrate each sensor using gas inlet flows of 100% oxygen and 100% N_2. Sensors were placed in manifold B for 6 hours and exposed to either dry air, 3% halothane in air, or air at 34 C with 100% relative humidity. At 2-hour intervals sensors were moved back to manifold A and sensor output was measured when exposed to 100% oxygen and 100% N_2.

time taken for the sensor to reach 63% of its final value as determined from a strip chart recording made using a chart speed of 4 in/min. All response times were measured at room temperature (22 C).

Oxygen sensor response to nitrous oxide was determined by exposing each of the 20 sensors to 100% O_2 (5 L/min flow) and adjusting the monitor gain so the output read 100%. The units were then placed for 5 minutes in 100% N_2, then in 100% N_2O, and finally in 100% N_2 (5 L/min flows). The sensor output was recorded after 5 minutes of exposure to each gas. The difference between the monitor reading in N_2O and the average of the two monitor readings in N_2 was reported as the N_2O response.

Results were analyzed by statistical multivariate analysis of variance using the MGLM program (Multivariate General Linear Models) (1). The data were organized to compare sensor readings vs time during the 6-hour exposure to either air, halothane, or humidity. A second analysis was performed to determine any difference between the performance of the brands of sensors.

Results

During exposure to room air for 6 hours, the data showed no significant drift in O_2 sensor output voltage (Table 1). These data were collected following a 1-hour warm-up period. Statistical analysis of sensor output vs time produced univariate F values with significance levels all less than 0.61. Considering all groups and times jointly, there was no significant change in sensor output and no difference between sensor brands. During the 1st hour of operation there was no significant change in output as shown in Table 4.

TABLE 1
Oxygen Sensor Reading following Exposure to Dry Air*

Time	Beckman	Critikon	Teledyne	IL
hr				
0	100.0	100.0	100.0	100.0
2	100.3 ± 0.54	100.8 ± 1.92	99.0 ± 0.74	99.5 ± 1.05
4	100.2 ± 0.54	101.3 ± 2.85	98.8 ± 1.22	99.7 ± 0.59
6	100.2 ± 0.58	101.1 ± 3.03	98.9 ± 1.22	99.4 ± 1.06

* Values are means ± 1 SD. Oxygen sensor reading when placed in 100% O_2 following exposure to dry room air for 2, 4, and 6 hours.

Exposure to 3% halothane for 6 hours produced the results shown in Table 2. To obtain readings the sensors were returned to manifold A and exposed to 100% N_2 and 100% O_2. This procedure circumvented the dilution effect of halothane on oxygen partial pressure and allowed isolation of the long-term effect of halothane on the sensor performance. Statistical analysis produced significant univariate F values ($p < 0.05$) for those means in Table 2 identified by a dagger. Although these changes are statistically significant, it is not likely that they are clinically important. The likelihood ratio test showed significant p values for the Critikon and Teledyne sensors. These values were $F = 11.2$ with 3, 10 df and a $p = 0.0019$ for the Critikon, and $F = 20.5$ with 3, 10 df and a $p = 0.003$ for the Teledyne sensors.
Teledyne sensors.

Exposing the 20 oxygen sensors to an environment containing air at 34 C with 100% relative humidity produced the results shown in Table 3. These results show the O_2 sensor output after removal from the high humidity environment and placement in dry 100% O_2. Given that water vapor and condensate have no physical effect on the sensor performance, each sensor should read 100. The likelihood ratio test showed a significant water vapor effect on the performance of the Beckman OM-10 sensor ($F = 23.2$ with 3, 14 df and a p value of 0.0001). Although the other sensors had periods when the output was significantly different from the control level (indicated by a dagger in Table 3), statistical analysis showed no overall effect.

Table 4 lists the N_2O effect and response times for the four brands of O_2 sensors tested. N_2O had very little effect on any of the sensors. Sensor response times were not changed significantly following 6 hours of exposure to 100% relative humidity.

Discussion

The intent of this study was to evaluate the performance of several commercially available oxygen

TABLE 2

Oxygen Sensor Reading following Exposure to 3% Halothane*

Time	Beckman	Critikon	Teledyne	IL
hr				
0	100.0	100.0	100.0	100.0
2	100.2 ± 0.99	102.3† ± 1.93	98.5 ± 0.59	98.8 ± 1.11
4	100.0 ± 1.27	103.2† ± 2.01	97.3† ± 0.83	98.6 ± 1.23
6	100.0 ± 1.45	103.3† ± 2.03	97.4† ± 0.38	99.5 ± 1.10

* Values are means ± 1 SD. Oxygen sensor reading when placed in 100% O_2 following an exposure to 3% halothane in air for 2, 4, and 6 hours.

† Indicates a statistically significant difference from 100 at the $p < 0.05$ level using multivariate analysis of variance.

TABLE 3

Oxygen Sensor Reading following Exposure to High Humidity*

Time	Beckman	Critikon	Teledyne	IL
hr				
0	100.0	100.0	100.0	100.0
2	81.2† ± 12.68	97.5 ± 1.92	97.3 ± 2.41	92.6† ± 6.66
4	81.0† ± 10.45	97.3 ± 3.58	93.2† ± 1.27	96.5 ± 0.32
6	79.8† ± 30.17	97.4 ± 4.41	93.8 ± 2.28	98.6 ± 1.04

* Values are means ± 1 SD. Oxygen sensor reading when placed in 100% O_2 following exposure to air with 100% relative humidity at 34° C for 2, 4 and 6 hours.

† Indicates a statistically significant difference from 100 at the $p < 0.05$ level using multivariate analysis of variance.

TABLE 4

Oxygen Sensor Performance Data*

	Beckman	Critikon	Teledyne	IL
Oxygen sensor reading when placed in 100% oxygen after 1st hr of operation	100.4 ± 0.0149	100.4 ± 0.0176	99.8 ± 0.035	99.8 ± 0.0079
Nitrous oxide (100%) effect	0.17 ± 0.22	0.36 ± 0.81	−0.12 ± 0.11	1.16 ± 1.84
Sensor response time (sec)	10.1 ± 0.17	5.1 ± 0.53	20.6 ± 3.9	2.85 ± 0.87
Response time following 6-hr exposure to 100% relative humidity (sec)	10.9 ± 0.46	5.1 ± 0.29	24.6 ± 5.8	3.7 ± 2.0

* Values are means ± 1 SD.

monitors under conditions normally found in the operating room (2, 3). When used for monitoring during anesthesia, an oxygen sensor is exposed for several hours to gases containing nitrous oxide, halothane, high humidity, and elevated temperature. This study was designed to quantify separately the effect of each of these gas components on oxygen sensor performance (4–6). The experimental method simulated the conditions in the operating room, an initial calibration at room temperature, and the continuous use for 6 hours in gases containing 3% halothane, 100% humidity, N_2O, and temperatures reaching 34 C with gas flows of 5 L/min.

When used in room air at constant temperature all sensors were found to be extremely stable with no significant change in sensor gain over a 7-hour period. Initially it was thought that the sensor output would change significantly during the 1st hour of use as the sensor warmed-up. The average drift during the 1st hour was found to be less than 0.5%. The 10 minutes required in this study for initial calibration may have been a sufficiently long warm-up period.

In this study we found a negligible N_2O effect. Halothane had a statistically significant effect on the Critikon and Teledyne sensors. The Critikon and Teledyne sensors' output drift rates were higher in a halothane-air mixture than in air alone suggesting a halothane effect. This effect may be caused by the diffusion of the halothane molecule into the oxygen-permeable membrane. It should be noted that the experimental design stressed the system by 6 hours of exposure to 3% halothane, a situation not commonly found clinically. Moreover, during routine clinical monitoring, an average change of less than

4.0% of reading as measured in this study would not be of clinical significance.

High humidity severely affected the performance of only the Beckman sensor. Because the Beckman sensor has a small recessed membrane, the membrane can be quickly covered by condensate when exposed to a high humidity environment. In this study the Beckman sensor's output fell by an average of 19% after less than 2 hours of exposure to a high humidity environment. Because of this water vapor effect, the Beckman sensor is not recommended for use in a closed or semiclosed circle system. It is an extremely stable sensor, and it has a much longer lifetime than the other sensors tested and could be used appropriately in the dry fresh gas inflow line or the inspired limb of a non-rebreathing circuit.

It is fortunate that failure of the Beckman sensor occurs in the direction of safety with the sensor reading a concentration that is lower than the actual oxygen concentration. This fact should prevent delivery of a hypoxic mixture. In contrast, a previously reported hazard (low batteries and N_2O) reported failure occurring in the other direction (6).

Most of the oxygen monitors marketed for use in the operating room contain one of the four sensors used in this study. We are aware of two sensors that have become available since we began our study: (*a*) Teledyne now makes a polarographic sensor; the monitor is being distributed by Ventronics, Inc, and (*b*) Catalyst Research Corp is producing a new fuel cell oxygen sensor. As new oxygen sensors are marketed, our hope is that they will be tested and evaluated under conditions found in the operating room.

The results of this study indicate that the Critikon, Teledyne, and IL sensors are appropriate for operating room monitoring of oxygen concentration. Their use is strongly advised as an extra margin of safety on all anesthesia cases.

REFERENCES

1. Morrison DF. Multivariate statistical methods. 2nd ed. New York: McGraw-Hill Book Co, 1976.
2. Schneider AJL, Kreul JF, Zollinger RM Jr. Patient monitoring in the operating room—an anesthetist's viewpoint. Med Instrum 1976;10:105–109.
3. Gorsky BH, Hall RL, Redford JE. A compromise of closed system anesthesia. Anesth Analg 1978;57:18–24.
4. Dent JG, Netter KJ. Errors in oxygen tension measurements caused by halothane. Br J Anaesth 1976;48:195–197.
5. Severinghaus JW, Weiskopf RB, Nishimura M, Bradley AF. Oxygen electrode errors due to polarographic reduction of halothane. J Appl Physiol 1971;31:640–642.
6. Piernan S, Roizen MF, Severinghaus JW. Oxygen analyzer dangerous—senses nitrous oxide as battery fails. Anesthesiology 1979;50:146–149.

ANESTH ANALG
60:57-58, 1981

Discontinuance of Nitrous Oxide Does Not Prevent Tension Pneumocephalus

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Tension pneumocephalus after posterior fossa craniotomy in the sitting position is not uncommon, and the deleterious effects of nitrous oxide have been implicated in the pathogenesis of this problem (1-4). We demonstrate here that this potentially life-threatening complication may occur even when nitrous oxide has been discontinued in an attempt to avoid the problem.

Case Report

A 9-year-old, 30 kg, white girl was admitted for evaluation of an acute onset of malaise, vomiting, and seizure activity which rapidly progressed to coma. On physical examination, the patient was febrile and comatose with mild decerebrate posturing. Pupils were pinpoint and nonreactive. Cranial nerve examination revealed symmetrical facies with absent gag and corneal reflexes. Deep tendon and oculocephalic reflexes were absent. The rest of the physical examination was normal. Computed tomography (CT) scan showed massive intraventricular hemorrhage. Carotid arteriograms revealed a posterior fossa arteriovenous malformation. A ventriculostomy was performed and treatment with aminocaproic acid, phenobarbital, dexamethasone, cimetidine, methacillin, and chloramphenicol was initiated. Ten days after admission, a Hakin standard valve ventriculoperitoneal shunt was inserted. The patient's mental status improved such that she could occasionally respond to simple commands. A posterior fossa craniotomy and resection of the arteriovenous malformation was scheduled on the 44th hospital day. Preoperative CT scan and skull x-ray showed no intracranial air.

Anesthesia was induced with sodium thiopental, 100 mg, and maintained with diazepam, fentanyl, and 66% nitrous oxide in oxygen. Endotracheal intubation was facilitated with pancuronium and controlled hyperventilation was instituted. A lumbar subarachnoid drain was inserted and the patient was then placed in the sitting position. Surgery progressed without incident until midway through the procedure when venous air embolism was evidenced by a change in the precordial Doppler signal, a decrease in $P_E CO_2$, and an increase in Pa_{CO_2}. The patient was given 100% oxygen. Aspiration through the right atrial catheter was negative for air. Blood pressure remained stable and $P_E CO_2$ returned to normal within 10 minutes. Nitrous oxide, 66%, was resumed, but was discontinued ½ hour before dural closure. Total duration of exposure to N_2O was 5½ hours. At the end of the operation the patient was taken to the neurosurgical intensive care unit where controlled ventilation with 100% O_2 was maintained. Two hours after arrival in the intensive care unit the patient developed a right hemiparesis and dilated left pupil. An emergency CT scan showed a large frontal pneumocephalus (Figure). This was released by bilateral twist drill holes in the cranium. The procedure was noted "to be productive of gas under pressure." The hemiparesis resolved over the ensuing 12 hours and the left pupil returned to normal after 2 days. The remainder of the postoperative course was unremarkable.

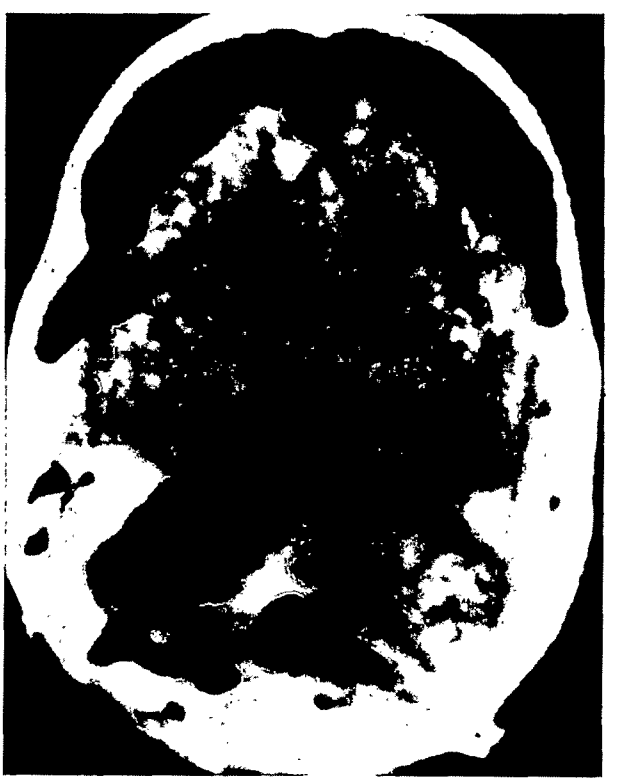


FIGURE. Postoperative CT scan showing large frontal pneumocephalus.

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Received from the Department of Anesthesiology, University of Virginia Medical Center, Charlottesville, Virginia. Accepted for publication September 28, 1980.
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The patient's mental status remained unchanged from the preoperative state.

Discussion

Nitrous oxide anesthesia has been implicated in the development of tension pneumocephalus during craniotomy and pneumoencephalography. Recently, several cases of tension pneumocephalus have been reported following posterior fossa exploration in the sitting position (1–4). All of these operations were performed with nitrous oxide anesthesia, and the circumstances implicate nitrous oxide as a causative factor in the development of postoperative pneumocephalus. In the present case, however, nitrous oxide was discontinued before dural closure in an effort to prevent postoperative tension pneumocephalus.

Tension pneumocephalus following this type of surgery has been attributed to several factors. The effects of gravity allow the brain to settle in the cranial vault as cerebrospinal fluid drains out of the inferior margin of the incision. In the present case this was exacerbated further by loss of cerebrospinal fluid through a lumbar subarachnoid drain, a ventriculoperitoneal shunt, and incision into the fourth ventricle. Diminution of brain volume by the use of mannitol, hyperventilation, steroids, head-up position, and contraction of intravascular volume associated with acute blood loss allows air to enter into the subdural space via the incision. After closure of the dura, reexpansion of the brain by rehydration, cerebral edema, replacement of depleted cerebrospinal fluid, and intravascular volume within the nonexpandable confines of the cranium may cause increased intracranial pressure. If reexpansion is associated with tension pneumocephalus, life-threatening sequalae may result from increased introcranial pressure and brain compression.

Diffusion of nitrous oxide into the air compartment also has been implicated in further increasing the size of a pneumocephalus. This phenomenon has been shown to occur in animals and man during air encephalography when increases in subarachnoid pressure occurred after the addition of nitrous oxide to the inspired gas mixture (5). The increase in intracranial pressure when N_2O is used during pneumoencephalography is maximal after 10 minutes of breathing nitrous oxide and returns to normal baseline levels within 10 minutes after discontinuing nitrous oxide. Thus, the potentiating effect of nitrous oxide should be maximal within a short period after dural closure and should resolve promptly after discontinuing nitrous oxide. In the present case, however, nitrous oxide was discontinued ½ hour before closing the dura and 1½ hours before the end of the procedure. We believe, therefore, that nitrous oxide probably may not play a major role in postoperative tension pneumocephalus. In fact, it may be advantageous to maintain anesthesia with high inspired concentrations of nitrous oxide until dural closure so that a pneumocephalus that formed intraoperatively would contain nitrous oxide that would then be reabsorbed rapidly when nitrous oxide was discontinued. This hypothesis, however, will require verification in an animal model.

In our experience, pneumocephalus is often seen after craniotomy. The progression to a tension pneumocephalus, however, may be masked by the effects of anesthesia early in the postoperative period. We recommend an immediate postoperative skull x-ray for early diagnosis and/or insertion of a subarachnoid pressure monitor that would not only indicate development of the tension pneumocephalus by an increase in intracranial pressure, but would also permit treatment by drainage. Early diagnosis of this condition can only be accomplished if the physician maintains a high index of suspicion following craniotomy, particularly when it has been performed in the sitting position. Nitrous oxide may not be a significant factor in the pathogenesis of tension pneumocephalus appearing in the postoperative period. Further studies substantiating this conclusion are needed.

REFERENCES

1. Kitahata LM, Katz VD. Tension pneumocephalus after posterior fossa craniotomy: a complication of the sitting position. Anesthesiology 1976;44:448–450.
2. Lunsford LD, Maroon JC, Sheptak PE, et al. Subdural tension pneumocephalus: report of two cases. J Neurosurg 1979;50: 525–527.
3. Mallamo JT, Hubbard RB, Boone SC, et al. Expansion of an air-filled subdural space during nitrous oxide anesthesia. Radiology 1975;115:369–372.
4. Hulett WB, Laing JW. Tension pneumocephalus in the sitting position. Anesthesiology 1976;45:578.
5. Saidman LJ, Eger EI. Change in cerebrospinal fluid pressure during pneumoencephalography under nitrous oxide anesthesia. Anesthesiology 1965;26:67–72.
6. Markham JW. The clinical features of pneumocephalus based upon a survey of 284 cases with report of 11 additional cases. Acta Neurochir (Wien) 1967;16:1–78.

ANESTH ANALG
60:59-60, 1981

Coincidental Fetal and Maternal Heart Block

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Continuous direct fetal ECG monitoring allows the intrapartum diagnosis of fetal arrhythmias (1). Its increased use has been accompanied by a parallel increase in the cesarean section rate. This trend means continuing and increasing involvement of anesthesiologists in the delivery suite. We recently encountered a case in which a fetal monitoring device first obscured and later disclosed a fetal bradycardia, thus setting the stage for a cesarean delivery.

Case Report

A 22-year-old gravida 2, para 1, at 37 weeks of gestation presented in early labor with 2- to 3-cm cervical dilation, the fetal head at −2 station, and intact membranes. Her history failed to reveal systemic disease, previous surgery, or problems with this pregnancy. Family history was negative for previous anesthetic difficulties. Prenatal records revealed that the patient's father had a cardiac pacemaker, but the patient herself had no evidence of cardiac disease. Routine fetal heart auscultation was not remarkable.

Auscultation of the fetal heart by fetoscope proved unsatisfactory; therefore, an external ECG monitor was applied and revealed a fetal heart rate of approximately 140 beats per minute. Six hours later, after little additional cervical dilation, the membranes were ruptured and a fetal scalp electrode was applied. At this time the fetal heart rate was noted to be approximately 64. Auscultation and sonography confirmed the fetal bradycardia; thus we diagnosed severe fetal distress. The patient was quickly taken to the operating room for an emergency cesarean section. During preoxygenation of the patient, after maternal ECG electrodes were applied, a pattern of 2:1 heart block appeared for a few seconds. Uneventful general anesthesia with thiopental, succinylcholine, and nitrous oxide commenced immediately, and a vigorous 2.5-kg boy was delivered. Apgar scores at 1 and 5 minutes were 8 and 9, respectively, one off for heart rate at both times. Postoperative ECGs demonstrated intermittent 2:1 heart block in the mother and persistent 2:1 heart block in the infant.

Discussion

Electronic fetal heart rate monitoring may be accomplished directly with a scalp electrode or indirectly using ultrasound. The Corometrics model FMS-101B ultrastonic fetal heart monitor used in this case has the inherent limitation that it may double heart rates approaching 60 beats per minute by sensing both heart sounds as individual beats (Corometrics Operating Instruments Manual, p 28, Corometrics Medical Systems, Inc, North Haven, CT). Consequently, the monitor can obscure severe fetal bradycardia. When the scalp electrode demonstrated marked fetal bradycardia, to verify proper equipment function, an ultrasound device was quickly utilized and verified the bradycardia. Maternal blood pressure was normal and when changes in maternal position failed to alter the fetal heart pattern the patient underwent cesarean section. The significance of the few seconds of observed intermittent maternal 2:1 heart block was unknown, but the abrupt conversion of the fetal heart rate from 140 beats per minute to a sustained bradycardia of 64 beats per minute immediately following rupture of the membranes seemed ominous.

When the patient awakened sufficiently to answer questions in the recovery room, several facts came to light. After pointed questioning, the patient said that occasionally her heart rate slowed to approximately 50 beats per minute. This had never caused her to consult a physician because it had never produced any problems. An extensive family history including all body systems is rarely taken for obstetrical patients. Consequently, the history of her father's pacemaker implantation at a relatively young age was not focused upon. Since specific questioning of the patient provided no useful information concerning the exact nature of her father's disease, one of the authors (H.M.F.) consulted the father's physician and reviewed the father's microfilmed chart. We discovered that the father experienced progressive heart block beginning with first-degree block at age 18 and continuing through second-degree to third-degree block at age 24. The third-degree block was treated by a permanently implanted pacemaker.

We have been unable to find previous reports of either intrapartum association of maternal and fetal

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heart block, or the occurrence of a second-degree heart block in three successive generations. The association of apparent subclinical maternal collagen-vascular disease and congenital fetal heart block has been described (2), but no such disease was present in our case. Brief episodes of second-degree heart block may occur in normal young individuals with Valsalva, or bearing down, maneuvers which take place during labor and childbirth. Our patient never reached the stage of making expulsive efforts.

Should similar circumstances recur, a diligent search for p-waves on the oscilloscopic readout of the fetal heart monitor and sampling of fetal scalp blood for pH might provide support for watchful waiting with anticipated vaginal delivery. Such, however, would be the case only if accurate, in-depth family history, and a positive patient history of heart block were available within minutes of the discovery of fetal bradycardia.

When presented with sudden, severe fetal bradycardia, which represents one of the most urgent obstetrical emergencies, an expeditious cesarean delivery frequently provides the only means for delivering a healthy, undamaged baby.

REFERENCES

1. Young BK, Katz M, Klein SA. Intrapartum fetal cardiac arrhythmias. Obstet Gynecol 1979;54:427–432.
2. Reid RL, Pancham SR, Kean WF, Ford PM. Maternal and neonatal implications of congenital complete heart block in the fetus. Obstet Gynecol 1979;54:470–474.

Complications Associated with Ambulatory Surgery

A prospective study of 13,433 patients at a freestanding ambulatory surgical center was performed; 99.8% of the patients were followed up through the first two postoperative weeks. Patients were asked to complete and return a prepaid postcard 2 weeks following surgery. Nonresponders received telephone calls. All reports of complications were followed by requests for further information from the surgeon and from the patient. One hundred six medical, surgical, or anesthetic complications were identified in the patient population. No deaths occurred in the center, and there was no instance of cardiovascular collapse. Sixteen patients were transferred to a general hospital. Surgery and anesthesia performed in either the inpatient or outpatient setting may be associated with serious complications. Many surgical procedures can be performed as safely in the outpatient setting as in the hospital inpatient setting. *(Natof HE: Complications associated with ambulatory surgery. JAMA 1980;244:1116–1118)*

ANESTH ANALG
60:61-63, 1981

Experience with the Use of Nitroprusside and Subsequent Epidural Analgesia in a Pregnant Quadriplegic Patient

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Improvements in medical care have contributed to increased survival of patients with spinal cord injury (1). As a result anesthesiologists may be involved in providing care for an increasing number of patients with spinal cord injury. It has been observed that 85% of the patients with spinal cord injury at or above the T-5 level develop signs and symptoms of autonomic hyperreflexia (2, 3) in response to visceral dilation or noxious cutaneous stimulation. There have been reports of autonomic hyperreflexia developing during labor and delivery in pregnant paraplegic patients (4–6). The associated hypertensive response, if uncontrolled, may cause convulsions, cerebrovascular accident and even death (7). Recently Stirt et al (4) and Watson et al (5) reported on the successful use of continuous epidural analgesia during active labor to control hypertension in paraplegic mothers (5). This report describes the use of sodium nitroprusside (SNP) and subsequent administration of continuous epidural analgesia to attenuate the hypertensive response in a quadriplegic mother during induced delivery of a dead fetus.

Case Report

A 19-year-old gravida 1, para 0 white woman, weighing 62 kg, was admitted to the obstetrical intensive care unit for intra-amniotic prostaglandin F_2-alpha injection for uterine evacuation of a dead fetus of 20 weeks gestation.

Forty days previously the patient was rendered permanently quadriplegic as a result of complete transection of the cord at C-5 level following a gunshot wound to the posterior neck. Before the injury she had been in good health. Neurologic examination revealed complete loss of sensory, motor, and reflex function below C-5 level except for minimal return of flexor reflexes in the lower extremities. Supine blood pressure was 80/40 torr and heart rate 100 beats per minute. In view of the return of the flexor reflex activity, which may coincide with the return of autonomic hyperreflexia (2), preparations were made to treat the possible occurrence of autonomic hyperreflexia. An indwelling radial arterial catheter was placed for the continuous measurement of blood pressure. Considering the low blood pressure and the difficulty we might have in estimating and controlling the level of epidural analgesia, we elected to control any hypertensive response that might occur with the administration of SNP. As this patient had not exhibited signs of autonomic hyperreflexia earlier, we felt that the uterine contractions might not induce significant change in blood pressure.

The transabdominal intrauterine injection of prostaglandin F_2-alpha produced no change in blood pressure or heart rate. The subsequent introduction of a vaginal speculum for the placement of laminaria increased the systolic blood pressure to 170 from 80 torr and decreased heart rate to 60 from 100 beats per minute within 10 seconds.

The speculum was removed and SNP was infused (100 μg/min). The laminaria was then inserted. During this time systolic blood pressure decreased to 120 torr. During the next 5 hours the uterine contractions were mild. Concomitant with the onset of more intense and prolonged contractions, the blood pressure increased to 200/70 torr and the patient complained of headache and nausea; facial flushing and profuse sweating were observed. Administration of SNP at the rate of 700 μg/min decreased the blood pressure and alleviated the symptoms. However, following cessation of uterine contractions, hypotension (70/30 torr) requiring vasopressor therapy occurred. Because of poor control of blood pressure and the possibility of prolonged need of administration of SNP with the risk of possible toxicity, it was decided to discontinue administration of SNP and institute continuous lumbar epidural analgesia to control the patient's autonomic hyperreflexia. The patient was prehydrated with 250 ml of Plasmanate and 500 ml of lactate Ringer's solution and an epidural catheter was placed in the L3–L4 epidural space using a Tuohy needle and the loss of resistance technique. Following hydration, the systolic blood pressure ranged from 90 torr between contractions to 150 torr during contractions. Five minutes following a test dose of 2 ml of 0.5% bupivacaine, 10 ml of 0.25% bupivacaine was administered. The level of sensory and sympathetic blockade could not be evaluated, but blood pressure stabilized at 110/50 torr and persisted at that level for the next 12 hours with mild uterine contractions continuing.

Ten milliliters of 0.25% bupivacaine was administered every 2 hours during that time. Vaginal examination, per-

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formed 16 hours after the commencement of epidural analgesia, showed products of conception protruding through the cervix. During further cervical dilation and protrusion of the fetus, the blood pressure remained elevated at 140/90 torr. Ten milliliters of 0.25% bupivacaine was administered every hour during that time. Three hours later the patient spontaneously expelled the products of conception. Following complete evacuation of the uterus, 20 units of oxytocin was administered intravenously; this produced a reduction in the size of the uterus. The blood pressure gradually decreased to 80/40 torr. The patient was observed for 6 hours following the procedure and the blood pressure remained stable during that time.

Discussion

Stirt et al (4) and Watson et al (5) reported on the successful use of continuous lumbar epidural analgesia to control autonomic hyperreflexia in two pregnant patients with spinal cord injury above T-5 levels. Their patients had been paraplegic for some years before the onset of labor and had shown signs of autonomic hyperreflexia. In addition, before the institution of epidural analgesia, those patients were in active labor and had systolic pressures at 100 torr or more. In our patient, we were initially reluctant to administer epidural analgesia because of her low blood pressure of 80/40 torr. We also felt that the administration of SNP would control any elevation in blood pressure should it occur.

In nonpregnant patients with high spinal cord injury successful control of autonomic hyperreflexia has been accomplished with intravenous administration of ganglionic blocking drugs (8). SNP has, however, advantages over trimethaphan or nitroglycerin. For example, in contrast to trimethaphan, SNP does not induce significant tachycardia during hypotension. In patients with high spinal cord injury, bradycardia may be the only compensatory mechanism for the hypertensive response to visceral stimulation. The low pseudocholinesterase levels that are observed in pregnant patients might also affect the effect and toxicity of trimethaphan. Snyder et al (9) reported on the use of nitroglycerin to control hypertension in a preeclamptic patient. In their patient reduction of blood pressure from 230/110 to 160/80 torr was accomplished by administration of intravenous nitroglycerin before induction of anesthesia. However, the blood pressure increased to 180/80 torr following endotracheal intubation. Fahmy (10) compared cardiovascular effects of nitroglycerin with those of SNP in patients receiving general anesthesia and noted that similar reductions in systolic blood pressure occurred with both agents, but that higher diastolic blood pressures were associated with nitroglycerin. He also noted that return to baseline blood pressure, following termination of administration, was slower following nitroglycerin. Landry et al (11) reported that nitroglycerin infusion (1 μg/kg/min) produced no significant hemodynamic alterations in seven patients.

In a pregnant patient with a living fetus, serious consideration should be given to the possible adverse effects antihypertensive drugs might have on the fetus and the newborn infant. Based on the observation in animals by Lewis et al (12) of high cyanide levels in the fetus following maternal administration of large doses (unspecified) of SNP, Snyder cautions against use of large doses of SNP in mothers (9). However, Lewis et al (12) did not observe significant cyanide levels in fetuses of animals that received low doses of SNP.

In a quadriplegic patient, utilizing simultaneous measurement of uterine activity and blood pressure, Rossier et al (13) noted significant increase in blood pressure during and decrease following uterine contractions. It is also known that the vasculature is very sensitive in these patients (14). This may explain the variable response to SNP that was observed in our patient. We feel that similar, uncontrollable responses are likely to be observed with the use of other antihypertensive drugs such as nitroglycerin and trimethaphan. Based on the difficulties we encountered in controlling the blood pressure with the administration of SNP in our patient, we agree with Stirt et al (4), in recommending continuous epidural analgesia as a more effective and reliable method of controlling autonomic hyperreflexia in pregnant patients with high spinal cord injury.

Since institution of epidural analgesia preceded by intravenous hydration does not cause further reduction in blood pressure, as we observed in our patient, the low preanesthestic blood pressure that is frequently observed in these patients should not discourage the use of epidural analgesia.

In quadriplegic patients with some return of reflex activity in 3 weeks to 3 months after initial injury, the evaluation of tendon reflexes may be utilized to estimate the level of epidural block. A larger "top up" volume (10 to 15 ml) than normally used (6 to 8 ml) should be administered to block effectively the sympathetic response to visceral stimulation. Since dramatic changes in blood pressure occur along with uterine contractions, intra-arterial blood pressure monitoring is essential in these patients.

In summary, we have described the difficulties encountered in controlling autonomic hyperreflexia

with SNP in a pregnant quadriplegic patient. The efficacy of continuous epidural analgesia for this purpose is reconfirmed and recommended.

ACKNOWLEDGMENT

The authors thank Dr. Robert K. Stoelting, Professor and Chairman, Department of Anesthesiology, Indiana University School of Medicine, for his helpful suggestion in the preparation of this paper.

REFERENCES

1. McMichan JC, Michel L, Westbrook PR. Pulmonary dysfunction following traumatic quadriplegia. JAMA 1980;243:528–531.
2. Desmond J. Paraplegia: problems confronting the anaesthesiologist. Can Anaesth Soc J 1970;17:435–451.
3. Guttmann L, Wititteridge D. The treatment and prognosis of traumatic paraplegia. Proc Roy Soc Med 1947;40:219–227.
4. Stirt JA, Marco A, Conklin KA. Obstetric anesthesia for a quadriplegic patient with autonomic hyperreflexia. Anesthesiology 1979;51:560–562.
5. Watson DW, Downey GO. Epidural anesthesia for labor and delivery of twins of a paraplegic mother. Anesthesiology 1980;52:259–261.
6. Gioller H, Paeslack V. Our experiences about pregnancy and delivery of the paraplegic woman. Paraplegia 1970;8:161–166.
7. Kwrnick NB. Autonomic hyperreflexia and its control with spinal cord lesions. Ann Intern Med 1956;44:678–686.
8. Ciliberbi BJ, Goldfein J, Rovenstine EA. Hypertension during anesthesia in patients with spinal cord injuries. Anesthesiology 1954;15:273–279.
9. Snyder SW, Wheeler AS, James FM. The use of nitroglycerin to control severe hypertension of pregnancy during cesarean section. Anesthesiology 1979;51:563–564.
10. Fahmy NR. Nitroglycerin as a hypotensive drug during general anesthesia. Anesthesiology 1978;49:17–20.
11. Landry LD, Philbin DM, Clifton EW, Verlee TR, Levine FH. Hemodynamic effects of intravenous nitroglycerin in patients with coronary artery disease. Anesthesiology 1979;51:S69.
12. Lewis PE, Cefalo RC, Naulty JS, Rodkey FL. Placental transfer and fetal toxicity of sodium nitroprusside. Gynecol Invest 1977;8:46.
13. Rossier AB, Ruffieux M, Ziegler WH. Pregnancy and labour in high traumatic spinal cord lesions. Paraplegia 1969;7:210–216.
14. Debarge O, Christensen NJ, Corbett JL, Eidelman BH, Frankel HL, Mathias CJ. Plasma catecholomines in tetraplegics. Paraplegia 1974;12:44–49.

Intracranial Pressure during Nitroglycerin-Induced Hypotension

Nitroglycerin was given intravenously to five anesthetized, hyperventilated (Pa_{CO_2} 25 to 30 torr) patients undergoing craniotomy. The patients were undergoing craniotomy for vascular tumor resection or excision of arteriovenous malformations. Before surgery there were no clinical signs of increased intracranial pressure (ICP). Prior to induction of general anesthesia, a subarachnoid screw and an indwelling radial artery catheter were inserted using local anesthesia. Anesthesia was induced with thiopental and maintained with nitrous oxide and fentanyl. Pancuronium was used for intubation. During the nitroglycerin infusion, as mean arterial pressure (MAP) decreased from 104.4 ± 4.0 (SE) to 69.0 ± 1.8 torr, ICP increased from 14.2 ± 0.7 to 30.8 ± 1.1 torr. Cerebral perfusion pressure decreased from 90.2 ± 3.6 to 38.2 ± 2.3 torr ($p < 0.0005$). The nitroglycerin-induced ICP increase appears to be due to capacitance vessel dilation within the relatively noncompliant cranial cavity, with subsequent cerebral blood volume increase. The authors recommend that nitroglycerin and other cerebral vasodilators be administered only after methods to improve intracranial compliance, such as diuretics and hyperventilation, have been instituted, or after the dura has been opened. *(Cottrell JE, Gupta B, Rappaport H, Turndorf H, Ransohoff J, Flamm ES: Intracranial pressure during nitroglycerin-induced hypotension. J Neurosurg 1980;53:309–311)*

ANESTH ANALG
60:64-65, 1981

Morphine-Induced Respiratory Depression following Bilateral Carotid Endarterectomy

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Severe respiratory depression was observed after preanesthetic medication with morphine and scopolamine in an adult patient with chronic obstructive pulmonary disease who 1 month earlier had been premedicated with the same combination without incident. In the intervening period, however, the patient had undergone a bilateral carotid endarterectomy. We postulate that loss of carotid body chemoreceptor function after the bilateral carotid endarterectomy (1) produced the respiratory depression associated with administration of morphine.

Case Report

A 66-year-old woman was admitted for increasing mitral insufficiency. Over the past 3 years she had noted increasing exertional dyspnea, chest tightness, and irregular heart beats. Three months before admission, the patient had a cerebrovascular accident from which she recovered with minimum residual neurologic deficits. Carotid angiography showed bilateral narrowing of the internal carotids near their bifurcation. Past medical history was otherwise unremarkable. On admission the patient was alert and in no distress. Neurologic examination revealed only the previously noted residual from the cerebrovascular accident (slurred speech and tongue deviation). Chest x-ray showed cardiomegaly; electrocardiogram showed atrial fibrillation with a ventricular rate of 84 beats per minute; and cardiac catheterization showed a pulmonary arterial pressure of 75/35 torr with a mean pulmonary capillary wedge pressure of 29 torr and V waves of 45 torr. Cardiac output was 3.6 L/min with 4+ mitral regurgitation. No coronary arterial disease was seen on angiography. Pulmonary function tests showed an FVC of 1.85 L (60% of the predicted value), an FEV_1 of 1.15 L (51% of the predicted value), an FEV_1/VC of 62%, MMEF 0.66 L/sec (26% of the predicted value), and FRC of 2.48 L (79% of the predicted value). Also, there was significant reduction in diffusing capacity (61% of the predicted value). Arterial blood gas determinations while breathing room air showed a pH of 7.45, Pa_{CO_2} of 42 torr, and Pa_{O_2} of 54 torr.

Because of the bilateral carotid stenosis, the patient was advised to undergo bilateral carotid endarterectomies before replacement of the mitral valve. Right carotid endarterectomy was performed following premedication with morphine, 6 mg, and scopolamine, 0.3 mg. Anesthesia and surgery were uneventful and the patient made a rapid recovery. Arterial blood gases measured in the postoperative period showed a pH of 7.41, Pa_{O_2} 80 torr, and Pa_{CO_2} of 35 torr while breathing room air with nasal oxygen. One week later the patient underwent the left carotid endarterectomy, this time with hydroxyzine, 75 mg, for premedication. Again, the surgery and anesthesia were uneventful and the patient made a rapid recovery.

Three weeks later the patient was scheduled for mitral valve replacement. All preoperative medications (digoxin, furosemide, and potassium) were discontinued the night before surgery. Premedication consisted of intramuscular morphine, 6 mg, and scopolamine, 0.3 mg. Approximately 10 minutes after being premedicated, the patient was found to be cyanotic and obtunded with a respiratory rate of 4 to 5/min. Assisted ventilation with O_2 was immediately instituted and no further resuscitation was required. Chest x-ray immediately following this episode was unchanged, as was the electrocardiogram. In view of her stable condition, it was decided to proceed with inhalation anesthesia and surgery. During the transfer to the operating room, the patient could be easily aroused, but needed intermittent stimulation and vocal encouragement to ensure an adequate respiratory rate. Subsequent anesthesia and surgery were uneventful. Postoperative course was complicated by mediastinal infection and the need for prolonged ventilatory support. Pain was controlled early in the postoperative period while respirations were being controlled with 2 to 3 mg of morphine intravenously. Neither analgesics nor sedatives were required after the patient was weaned from the ventilator. The patient was discharged 2 months after surgery in satisfactory condition.

Discussion

Morphine depresses ventilation mainly through a central mechanism; the central chemoreceptor response to carbon dioxide is depressed while the peripheral chemoreceptor response to hypoxemia re-

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Received from the Anesthesiology Section, Clinical Center, National Institutes of Health, Bethesda, Maryland and the Anesthesia Department, Georgetown University School of Medicine, Washington, DC. Accepted for publication October 6, 1980.

Reprint requests to Dr. Lee, Department of Anesthesia, Georgetown University Hospital, 3800 Reservoir Road, NW, Washington, DC 20007.

mains unaffected (2). Respiratory depression after morphine premedication is well recognized. However, the respiratory depression with routine doses of morphine is of clinically insignificant magnitude. Normally, the resting Pa_{CO_2} is elevated approximately 3 torr after 10 mg of morphine in a healthy adult (3). Although carbon dioxide retention and hypoxemia resulting from hypoventilation with morphine may be exaggerated in our patient because of her chronic obstructive pulmonary disease (4), the morphine premedication was well tolerated initially before the first carotid endarterectomy.

Bilateral carotid endarterectomy results in a loss of carotid body function with loss of the usual ventilatory or circulatory compensatory responses to hypoxemia. This may be a consequence of either direct damage to the carotid body or indirect damage to the neurologic or vascular supply of the carotid body (the common occipito-ascending pharyngeal trunk). The loss of the ventilatory response to hypoxia and the elevation of a resting Pa_{CO_2} may persist for up to 10 months after surgery (1).

In our patient the preoperative Pa_{CO_2} before the first endarterectomy was slightly elevated (42 torr) in spite of the low Pa_{O_2} (54 torr). The arterial blood gas tensions after the first carotid surgery did not show any elevation of resting Pa_{CO_2} (35 torr). These findings suggest that the slight elevation of the resting Pa_{CO_2} in the face of a low Pa_{O_2} may have been the result of loss of the hypoxic ventilatory response rather than a manifestation of chronic obstructive pulmonary disease alone. With intact carotid body function before carotid surgery, the centrally depressed ventilation with morphine was compensated for when further arterial hypoxemia developed so that severe ventilatory depression was not seen. After the bilateral carotid endarterectomies, however, the morphine-induced central ventilatory depression and subsequently hypoxemia were unchecked since the compensatory ventilatory response to hypoxia was abolished. This eventually led to clinical cyanosis and obtundation.

In view of the fact that the ventilatory response to hypoxemia may be lost for upward of 10 months after bilateral carotid endarterectomies, the choice of a narcotic as a premedication should be considered carefully in patients following this type of surgery, particularly in patients with chronic obstructive pulmonary disease.

REFERENCES

1. Wade JG, Larson CP, Hickey RF, et al. Effect of carotid endarterectomy on carotid chemoreceptor and baroreceptor function in man. N Engl J Med 1970;282:825–828.
2. Jaffe JH, Martin WR. Narcotic analgesics and antagonists. In: Goodman, LF, Gilman A, eds. The pharmacological basis of therapeutics (5th Ed). New York: Macmillan, 1975:245–283.
3. Loeschcke HH, Sweel A, Kough RH, et al. The effect of morphine and of meperidine (Dolantin, Demerol) upon the respiratory response of normal men to low concentrations of inspired carbon dioxide. J Pharmacol Exp Ther 1953;108:375–383.
4. Lane DJ, Howell JBL. Relationship between sensitivity to carbon dioxide and clinical features in patients with chronic airway obstruction. Thorax 1970;25:150–159.

letters TO THE EDITOR

Endotracheal Tube in Place Passing through Bite Block

To the Editor:

The modification of an oral airway to serve as a bite block reported recently by Schwartz and Lee (1) has prompted me to report my own experience with a simple device to be used as a bite block and endotracheal tube stabilizer.

Approximately 2.5 cm of the barrel of a 10-ml plastic disposable syringe is cut off near the flange and the cut ends are smoothed. Two heavy sutures are passed through the flange. An endotracheal tube with internal diameter up to 10 mm can be easily passed through this modified bite block before intubating the trachea (Figure). Once the endotracheal tube is in place the bite block can be positioned between the molar teeth, thus allowing the endotracheal tube to be stabilized in one or the other angle of the mouth. Endotracheal tube and heavy suture are either taped to the patient's cheek or tied around the neck. This simple device offers the advantage of comfort to the patient who requires prolonged intubation in the postoperative period and is often conscious. It makes suction of the oropharynx easier, is more economical than using a traditional oropharyngeal airway, and avoids compression of incisors and canine teeth.

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REFERENCE

1. Schwartz AJ, Lee KW. Modification of oral airway as bite block. Anesth Analg 1980;59: 225.

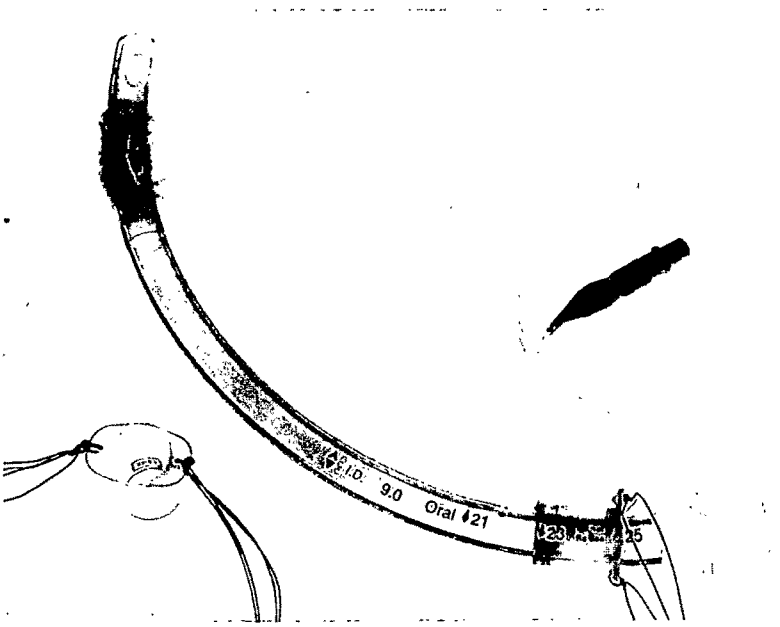


FIGURE. Endotracheal tube passing through modified bite block.

Valve Misassembly—Manually Operated Resuscitation Bag

To the Editor:

During management of a recent case of cardiac arrest, after initial ventilation with bag and mask, endotracheal intubation was performed. Breath sounds were diminished bilaterally, left more than right, and an inspiratory leak, noted around the cuff of the endotracheal tube, was not abolished by further inflation of the cuff. The endotracheal tube was replaced. Simultaneously, subclavian intravenous access attempts were being made.

The results of ventilation of the patient's lungs following reintubation were the same as before, although tube placement was confirmed by direct laryngoscopy. A pneumothorax subsequent to attempts at subclavian puncture was suspected. A cannula placed through the patient's chest wall produced hissing taken as confirmation of a tension pneumothorax. Breath sounds were still poor, and the leak around the cuff of the endotracheal tube persisted.

It became apparent that expiration was not occurring. Another resuscitation bag was substituted and immediately normal ventilation resulted.

Later, the Laerdal resuscitation bag originally used was disassembled. Two expiratory valve leaflets were present. One was correctly positioned on the gas exit side of the expiratory port apertures obscuring another leaflet on the gas inlet side of the expiratory port apertures which, in turn, was obstructing the expiratory pathway.

The self-inflating resuscitation bag is generally regarded as being a simple device for providing pulmonary

ventilation, and the Laerdal bag is a well designed unit that is difficult to assemble incorrectly. Two leaflets had apparently been fitted after cleaning.

A later design (Laerdal valve III) incorporates a right angle in a one-piece molding. Internal ridging makes accurate assembly easier and produces poorer valve competence with a misplaced leaflet. Newer leaflets are yellow instead of flesh-colored for easier recognition.

It is essential that after re-use, self-inflating resuscitation bags be tested for proper function during both expiration as well as inspiration. This is easily done by ventilation of a test lung such as an anesthesia reservoir bag.

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New Use for Swan-Ganz Introducer Wire

To the Editor:

Facilitation of difficult endotracheal intubation via cannulation of the cricothyroid membrane and passing a silk suture or CVP catheter is well known (1). The use of a Swan-Ganz introducer wire offers several advantages.

The technique may be done rapidly using a 16-gauge intravenous catheter to puncture the cricothyroid membrane. The stylet is withdrawn and the soft flexible end of a long Swan-Ganz introducer wire (USCI, Bard, Teflon-coated spring guide #007045, 120 cm) is passed by tilting the intravenous catheter to aim the wire through the vocal cords. The wire may then be passed into the oral pharynx and out the mouth or, with surprising ease, into the nasopharynx and out the nose; this obviates the use of laryngoscope and Magill forceps. An endotracheal tube is then placed over the wire and threaded into the trachea (Figure). The wire may then be withdrawn from either end. This leaves no suture tied to the eye of the endotracheal tube, which is an advantage in cases of prolonged intubation. If, as the tube nears the larynx, it hangs up on the epiglottis or the arytenoid cartilages, the endotracheal tube may be withdrawn and the wire inserted through the Murphy eye rather than the lumen of the endotracheal tube (2). The tube is then passed in the same fashion.

This technique eliminates several of the steps in the traditional technique of retrograde endotracheal intubation.

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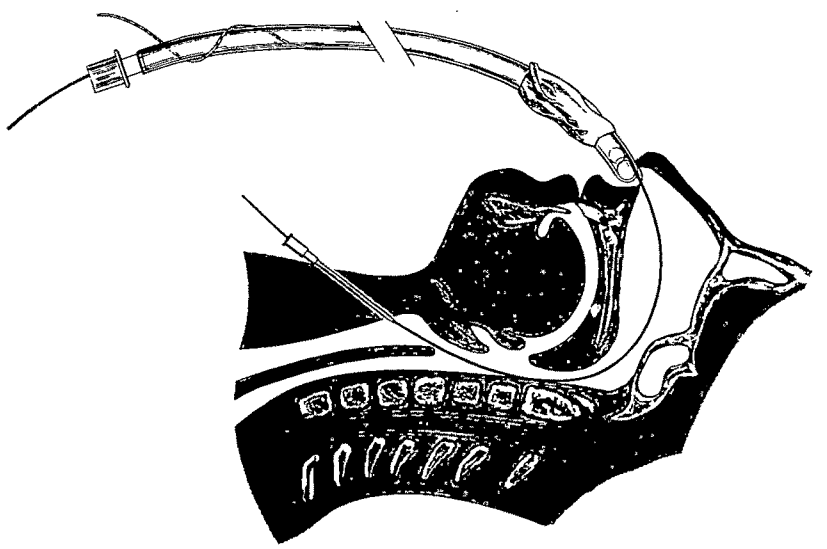


FIGURE. Swan-Ganz introducer wire passing through the vocal cords.

REFERENCES

1. Waters DJ. Guided blind endotracheal intubation. Anesthesia 1963;18:158–162.
2. Bourke D. Modification of retrograde guide for endotracheal intubation. Anesth Analg 1974;53:1013–1014.

Hemodynamic Monitoring with Pocket Calculators

To the Editor:

A simple method for easy calculation of hemodynamic parameters with the aid of a hand-held programmable calculator (TI-59, Texas Instruments Inc., Dallas, TX) was recently described by Barash and coworkers (1). The program is intended for use without a printer, which is particularly advantageous in a crowded area such as the operating room.

Different problems arise in the intensive care unit, and we have found a modified version of the original program to be useful.

First, input data are printed with labels (PC 100 C, Texas Instruments), avoiding the necessity of monitoring modules. Second, right-ventricle stroke work index is also derived, making the program appropriate for monitoring biventricular function during acute respiratory distress syndrome. Finally, all figures are approximated to the hundredth, which is adequate for clinical purposes.

The final print-out is as follows:

160. Ht
61.8 Wt
5.35 CO
60. P
78. BP
13. RAP
25. PAP
20. PCWP
1.64 BSA
3.26 CI
54.28 SVI
42.82 LVSW
8.86 RVSW
19.96 SVR
1.54 PVR

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REFERENCE

1. Barash PG, Chen Y, Kitahata LM, Kopriva CJ. The hemodynamic tracking system: a method of data management and guide for cardiovascular therapy. Anesth Analg 1980;59:169–74.

Bronchofiberscopic Jet Ventilation

To the Editor:

Recently a new technique for jet ventilation during bronchofiberscopy was introduced by Satyanarayana et al (1). They demonstrated that ventilation was adequate when the tip of the bronchofiberscope was placed 6 cm beyond the vocal cords. It was postulated that during the initial phase of jet inspiration a negative pressure was created causing an inflow of air through the vocal cords. This was confirmed by pressure measurements and by demonstrating a tracheal oxygen concentration of approximately 90%.

However, in clinical practice the tip of the bronchoscope must be introduced into the main bronchi in order to visualize the bronchial system. During the initial inspiratory phase a gas movement from the contralateral lung may then take place, thus resulting in an increased dead space and a decrease in the effective alveolar ventilation.

Second, if the bronchoscope is introduced further into the bronchial tree, then the increased resistance to outflow may result in an excessive pressure with subsequent risk of lung damage.

Until the clinical significance of these two situations has been elucidated, the method must be considered potentially hazardous and not recommended for daily routine bronchofiberscopy.

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REFERENCE

1. Satyanarayana T, Capan L, Ramanathan S, Chalon J, Turndorf H. Bronchofiberscopic jet ventilation. Anesth Analg 1980;59:350–354.

To the Editor:

Dr. Thomsen errs in his assumption that we recommended the bronchofiberscopic jet ventilation for routine diagnostic bronchoscopy. We merely described a reliable method for providing adequate prolonged tracheal ventilation (1). It is unnecessary to introduce the tip of the bronchoscope below the carina to accomplish this. Therefore, the hypothetical considerations of both cross entrainment of gases from the contralateral lung and barotrauma do not arise. Moreover, the development of pendeluft during unilateral bronchial jet ventilation remains to be proven. The occurrence of barotrauma during distal bronchial ventilation is not unique to our method and has been reported when the tip of the suction catheter used for jet ventilation is inadvertently advanced too far (2). If our method is adopted for routine endoscopy, jet inflation should be performed only when the tip of the instrument is in the trachea. Since it is possible to verify visually the location of the endoscope tip, one can avoid unilateral jet ventilation. The high Pa_{O_2} obtained with our method allows ample time for bronchial manipulation without the need for jet inflation in the distal bronchial tree.

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REFERENCES

1. Satyanarayana T, Capan L, Ramanathan S, Chalon J, and Turndorf H. Bronchofiberscopic jet ventilation. Anesth Analg 1980;59:350–354.
2. Chang JL, Bleyaert A, Bedger R. Unilateral pneumothorax following jet ventilation during general anesthesia. Anesthesiology. 1980;53:244–246.

book REVIEWS

Essential Noninvasive Monitoring in Anesthesia, edited by J. S. Gravenstein, R. S. Newbower, A. K. Ream, and N. T. Smith, New York, Grune & Stratton, 1980, 336 pp, $19.50.

In the 1970s, the practicing anesthesiologist saw a diverse growth in the invasive monitoring of the patient to obtain information regarding the status of milieu interior. The 1980s will probably see a growth in noninvasive monitoring during anesthesia. If the same information obtainable by invasive monitoring could be obtained by noninvasive monitoring, with the same reliability, most physicians would prefer noninvasion. This book on noninvasive monitoring in anesthesia is arranged in four sections dealing with (1) noninvasive blood pressure measurements, (2) electrocardiography in the operating room, (3) cutaneous tissue and respiratory gas measurements, and (4) failure to monitor.

As there is no absolute best way of noninvasive monitoring of a particular organ in the body, the physician should be familiar with the advantages and disadvantages of each of the monitoring systems and then be able to choose appropriately the system that works best in the given clinical situation. This book nearly achieves the goal of familiarizing the reader with various noninvasive systems available for monitoring organ systems during anesthesia and surgery.

Most of the chapters were written by nonphysicians who are involved with the development of noninvasive monitors. Some of the chapters, therefore, are highly technical, beyond the understanding of the average practicing anesthesiologist. Most of the chapters explain the design of various monitors, but they tell very little about the usage and limitations of the monitors in the clinical setting. For example, the chapter on the mass spectrometer deals with methods of measuring gases, but there is little about the clinical use of these measurements. Surprisingly, there is no mention of echocardiographic monitoring.

The chapter "Failure to Monitor" by Gravenstein is philosophical and thought provoking. He points out that although the anesthesiologist may use a multitude of monitors, unless he can analyze, synthesize, and apply the data according to the patient's needs, the monitors become useless. Extensive use of line drawings of equipment augment the description of monitors. This well written book is a good reference source for practicing anesthesiologists and residents in training who wish to know how the noninvasive monitor functions.

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Medical Problems and the Anaesthetist — Current Topics in Anaesthesia, Volume 4, by L. Kaufman and E. Sumner, Chicago, Year Book Medical Publishers, Inc, 1979, 156 pp, $32.95.

This almost pocket-size book is fourth in a series titled *Current Topics in Anaesthesia.* The British co-authors' stated intent is to provide up-to-date literature reviews to supplement comprehensive textbooks. The book consists of four sections: the cardiovascular system, the respiratory system, hematology, and the endocrine system, with half of the book devoted to endocrine disorders.

Brief discussions, with wide variation of detail, are presented on selected medical problems that complicate perianesthetic management. For example, in the 28 pages devoted to the cardiovascular system, 10 brief discussions, with references, are presented, whereas equal space is devoted to a discussion of pheochromocytoma in another section. A concise discussion of pulmonary pathophysiology focuses on preoperative assessment and preparation of the patient with pulmonary dysfunction. This section includes a rather detailed discussion of recent thoughts regarding asthma, giving general suggestions for anesthetic management. In the endocrine disorder section, pharmacology and pathophysiology are treated in greatest detail. American readers will note that not all drugs discussed are available on this side of the Atlantic and will recognize different approaches to perioperative management. An otherwise extensive discussion of pheochromocytoma inexplicably fails to mention enflurane in terms of anesthetic approach. A final section dealing with anemias outlines changes in conceptual approach to these disorders over the past decade, particularly regarding sickle cell disease. Much emphasis is placed on the significance of 2,3-diphosphoglycerate throughout this section.

The aim of the authors is realized in much of this book. Although in

some instances the depth of discussion appears excessively limited, overall the book will supplement standard texts for the busy anesthesiologist. For the inquisitive, recent (1970–1977) pertinent references are provided.

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Parenteral & Enteral Nutrition, by G. D. Phillips and C. L. Odgers, Adelaide, South Australia, University Relations Unit, The Flinders University of South Australia, 1980, 105 pp, $8.75.

There is a need for a practical guide for parenteral and enteral nutrition because of the rapid proliferation of literature concerning parenteral nutrition in the last few years. This book's introduction states that its aims are: (1) to present the principles of parenteral nutrition; (2) to elaborate on technical details; (3) to outline recent advances; and (4) to compare parenteral nutrition with tube feeding. This small book contains a vast amount of factual information; the aims of the monograph are fulfilled.

This book is a guide for medical students, intensive care unit (ICU) nurses, and physicians who occasionally use parenteral nutrition. The work is well edited and free of any gross errors. The authors are to be commended for a job well done and for fulfilling a definite need. One point is well taken, "Parenteral nutrition is inappropriate if it prolongs death rather than helps toward recovery," a thought our colleagues should ponder before instituting it.

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Anesthesia for Infants and Children, 4th ed, by R. M. Smith, St. Louis, CV Mosby Co, 1979, 702 pp, $45.00.

This book takes on the challenge of presenting a comprehensive review of all aspects of pediatric anesthesia, including pre- and postoperative management. The book is intended for use by practitioners at all levels of training and experience, and it succeeds quite well. The text in this edition has been expanded to include information on new developments in such areas as neonatal physiology, neurophysiology, and pediatric intensive care unit (ICU) function. Additions to the book are separate chapters on clinical management of urologic and ophthalmic surgery and an appendix. The organization of the text has been changed to a three-part format. Part 1 deals with theoretic and technical considerations; part 2 contains the clinical management of specific anesthetic considerations; and part 3 discusses allied topics. This format gives the reader a more organized approach to the practice of pediatric anesthesia.

The first section deals with physiologic differences between neonatal patients and adults, including a concise and easily understood chapter by Motoyama and Cook on respiratory physiology. This book also includes the topics of preoperative preparation of the child, hypotensive anesthesia, and anesthetic techniques, the latter being divided into chapters on monitoring, intubation, recovery, anesthesia systems, etc. The information ranges from occasional apparently obvious suggestions (learning the child's first name) to sophisticated descriptions of pediatric physiology. Diagrams and graphs are interspersed frequently serving a dual function of embellishing the text while resting the eye. The chapter on pediatric anesthesia systems is a particularly succinct review of a complex topic.

The second section deals with clinical management in specific areas of anesthesia. Here descriptions of surgical procedures are provided as well as suggested safe methods of anesthesia for a given procedure, with consideration given to the skills of both surgeon and anesthesiologist. Detailed suggestions are made concerning fluid management, choice of agent, and endotracheal intubation, etc for each major surgical procedure. The chapter on neurosurgical procedures is particularly helpful for those who do not practice neurosurgical anesthesia everyday, with a review of recent advances in knowledge in neurophysiology and pharmacology, practical suggestions in managing a child with an intracranial lesion for diagnostic procedures or surgery, and excellent illustrations of lesions and positioning.

Finally, a third section covers "allied topics," including fluid and electrolyte management, complications, mortality, and the role of the anesthesiologist in the pediatric ICU. This latter topic is an area that has expanded rapidly in sophistication during the past 10 years and offers a potentially exciting role to the pediatric anesthesiologist. The review offered here is a good beginning for the resident or practitioner who wishes to communicate intelligently with pediatric ICU staff, and is also a jumping off place for those who may wish to delve deeper and become more actively involved in the pediatric or neonatal ICU.

This is an ambitious work and generally succeeds in covering a vast amount of material in a readable format. Extensive references are listed at the end of each chapter; these include classic articles and recent reviews for those who wish to explore further. However, enough depth is offered so that the work can stand alone. One obvious area of recent advancement, which will perhaps merit its own section in the next edition, is the area of special problems of the premature infant, a subset of patients created by modern technology. *Anesthesia for Infants and Children* continues to be a textbook that deserves a place in the anesthesiologist's library.

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BOOK NOTES

Lecture Notes on Respiratory Disease, 2nd ed, by R. A. L. Brewis, St. Louis, Blackwell Scientific Publications, 1980, 312 pp, $17.75.

A concise basic review of pulmonary medicine. The second edition now includes multiple-choice questions. Easy to read, this book continues to serve as a sound introductory text to the subject.

Medical Examination Review, Volume 12—Anesthesiology, 5th ed, edited by T. J. DeKornfeld and M. D. Detmer, Garden City, NY, Medical Examination Publishing Co, Inc, 1980, 288 pp, $15.00.

This book is a collection of 1,060 questions pertinent to anesthesia. The topics covered are anatomy, physiology, physics, biochemistry, pharmacology, general anesthesia and specific muscle relaxants, local anesthetics and conduction anesthesia, complications, special procedures, respiratory care, legal considerations, and pediatrics. This fifth edition has fewer references, but includes 24 textbooks that are the accepted authorities in their fields, including the 1978 A.S.A. Refresher Course book. In addition, the book has all the answers with specific reference to those texts and a short, pertinent explanation with each answer. This latter feature is new with this edition and represents a worthwhile improvement as it allows perusing the questions and answers, a valuable learning experience even without access to the references. The book is an ideal study guide for those preparing for boards, as well as an up-to-date review of those basic sciences and clinical fields pertinent to anesthesia.

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BOOKS RECEIVED

Anesthesia in Obstetrics, by G. A. Albright, Menlo Park, CA, Addison-Wesley Publishing Co, Inc, 1978, 408 pp, $29.00.

Cardiac Arrest and CPR, by S. A. Budassi, J. J. Bander, L. Kimmerle, and K. F. Eie, Rockville, MD, Aspen Systems Corp, 1980, 202 pp, $24.50.

Neurosurgical Anaesthesia and Intensive Care, by T. V. Campkin and J. M. Turner, Woburn, MA, Butterworths, 1980, 267 pp, $49.95.

Neural Blockage, by M. J. Cousins and P. O. Bridenbaugh, Philadelphia, JB Lippincott Co, 1980, 754 pp, $95.00.

Medical Examination Review, Volume 12—Anesthesiology, 5th ed, edited by T. J. DeKornfeld and M. D. Detmer, Garden City, NY, Medical Examination Publishing Co, Inc, 1980, 288 pp, $15.00.

Molecular Mechanisms of Anesthesia—Progress in Anesthesiology, Volume 2, edited by B. R. Fink, New York, Raven Press, 1980, 528 pp, $48.50.

Manual of Cardiac Surgery, Volume 1, by B. J. Harlan, A. Starr, and F. M. Harwin, Secaucus, NJ, Springer-Verlag New York Inc, 1980, 204 pp, $112.00.

Basic and Clinical Sciences in Anesthesiology, 9th ed, by A. B. Tarrow and J. C. Erickson, Cedar Falls, IA, Lydette Publishing Co, 1980, 563 pp, $23.25.

Neuroanesthesia—Current Topics in Anaesthesia, Volume 3, by M. Marshall, Chicago, Year Book Medical Publishers, Inc, 1979, 78 pp, $18.95.

Erratum

In the paper "Afterload Reduction and Preload Augmentation Improve the Anesthetic Management of Patients with Cardiac Failure and Valvular Regurgitation" by J. Gilbert Stone et al (*Anesth Analg* 1980;59:37–42) there is an error on page 741, second paragraph, first sentence. The text should read: Nitroprusside, like any other vasodilator, increases venous capacitance.

A Guide for Authors

Manuscripts should be sent to:
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Editorial Policies

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Types of materials. The Journal publishes original articles, clinical reports, review articles, and letters to the editor. Original articles describe in 3000 words or less clinical or laboratory investigations. Clinical reports describe in 1000 words or less either (a) new and instructive case reports, or (b) anesthetic techniques or equipment of demonstrable originality, usefulness, and safety. Review articles of 2500 to 4000 words collate, describe, and evaluate previously published material for the establishment of new concepts. Letters to the editor, less than 300 words in length, include brief constructive comments concerning previously published articles or brief notations of general interest. Preliminary or incomplete reports are not accepted, nor are manuscripts containing fragments of material better incorporated into a single paper.

Peer review. All papers are reviewed by three or more referees. Acceptance is based upon significance, originality, and validity of the material presented. Every effort will be made to advise authors within 4 weeks whether papers are accepted, rejected, or need revision prior to further consideration for possible publication.

Legal and ethical considerations. Information or illustrations must not permit identification of patients. Reports describing data obtained from experiments performed in humans must contain a statement in the Methods that institutional approval of the investigation and informed consent were obtained. Reports describing data obtained from experiments performed in animals must clearly indicate that humane standards equal to those described by the American Physiological Society were employed.

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Manuscripts

Manuscripts must be prepared and submitted in the manner described in "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" as described in Annals of Internal Medicine 1979; 90: 95–9, and Lancet 1979; 1: 428–30.

Type manuscripts on white bond paper, 20.3 by 26.7 cm or 21.6 by 27.9 cm (8 by 10½ in or 8½ by 11 in) or ISO A4 (212 by 297 mm) with margins of at least 2.5 cm (1 in). Use double spacing throughout, including title page, abstract, text, acknowledgments, references, tables, and legends for illustrations.

Begin each of the following sections on separate pages: title page, abstract and key words, text, acknowledgments, references, tables (each table, complete with title and footnotes, on a separate page), and legends. Number pages consecutively, beginning with the title page. Type the page number in the upper right-hand corner of each page.

Illustrations must be good quality, unmounted glossy prints, usually 12.7 by 17.3 cm (5 by 7 in), but no larger than 20.3 by 25.4 cm (8 by 10 in).

Submit three copies of manuscript and figures in heavy-paper envelope. Submitted manuscript should be accompanied by covering letter, and permissions to reproduce previously published materials or to use illustrations that may identify subjects.

Authors should keep copies of everything submitted.

Title Page. The title page should contain [1] the title of the article, which should be concise but informative; [2] a short running head or footline of no more than 40 characters (count letters and spaces) placed at the foot of the title page and identified; [3] first name, middle initial, and last name of each author, with highest academic degree(s); [4] name of department(s) and institution(s) to which the work should be attributed; [5] disclaimers, if any; [6] name and address of author responsible for correspondence about the manuscript; [7] name and address of author to whom requests for reprints should be addressed, or statement that reprints will not be available from the author; [8] the source(s) of support in the form of grants, equipment, drugs, or all of these.

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Text. The text of observational and experimental articles is usually—but not necessarily—divided into sections with the headings Introduction, Methods, Results, and Discussion. Long articles may need subheadings within some sections to clarify their content, especially the Results and Discussion sections. Case reports and reviews do not require the above sections.

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When reporting experiments on human subjects, indicate whether the procedures followed were in accord with the ethical standards of the Committee on Human Experimentation of the institution in which the experiments were done or in accord with the Helsinki Declaration of 1975. When reporting experiments on animal subjects, indicate whether the institution's or the National Research Council's guide for the care and use of laboratory animals was followed. Identify precisely all drugs and chemicals used, including generic name(s), dosage(s), and route(s) of administration. Do not use patients' names, initials, or hospital numbers.

Include numbers of observations and the statistical significance of the findings when appropriate. Detailed statistical analyses, mathematical derivations, and the like may sometimes be suitably presented in the form of one or more appendixes.

Results. Present your results in logical sequence in the text, tables, and illustrations. Do not repeat in the text all the data in the tables and/or illustrations: emphasize or summarize only important observations.

Discussion. Emphasize the new and important aspects of the study and *conclusions* that follow from them. Do not repeat in detail data given in the Results section. Include in the Discussion the implications of the findings and their limitations and relate the observations to other relevant studies. Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not completely supported by your data. Avoid claiming priority and alluding to work that has not been completed. State new hypotheses when warranted, but clearly label them as such. Recommendations, when appropriate, may be included.

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Books and Other Monographs

3. Personal Author(s)

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5. Editor, Compiler, Chairman as Author

   Rhodes AJ, Van Rooyen CE, comps. Textbook of virology: for students and practitioners of medicine and the other health sciences. 5th ed. Baltimore: Williams & Wilkins, 1968.

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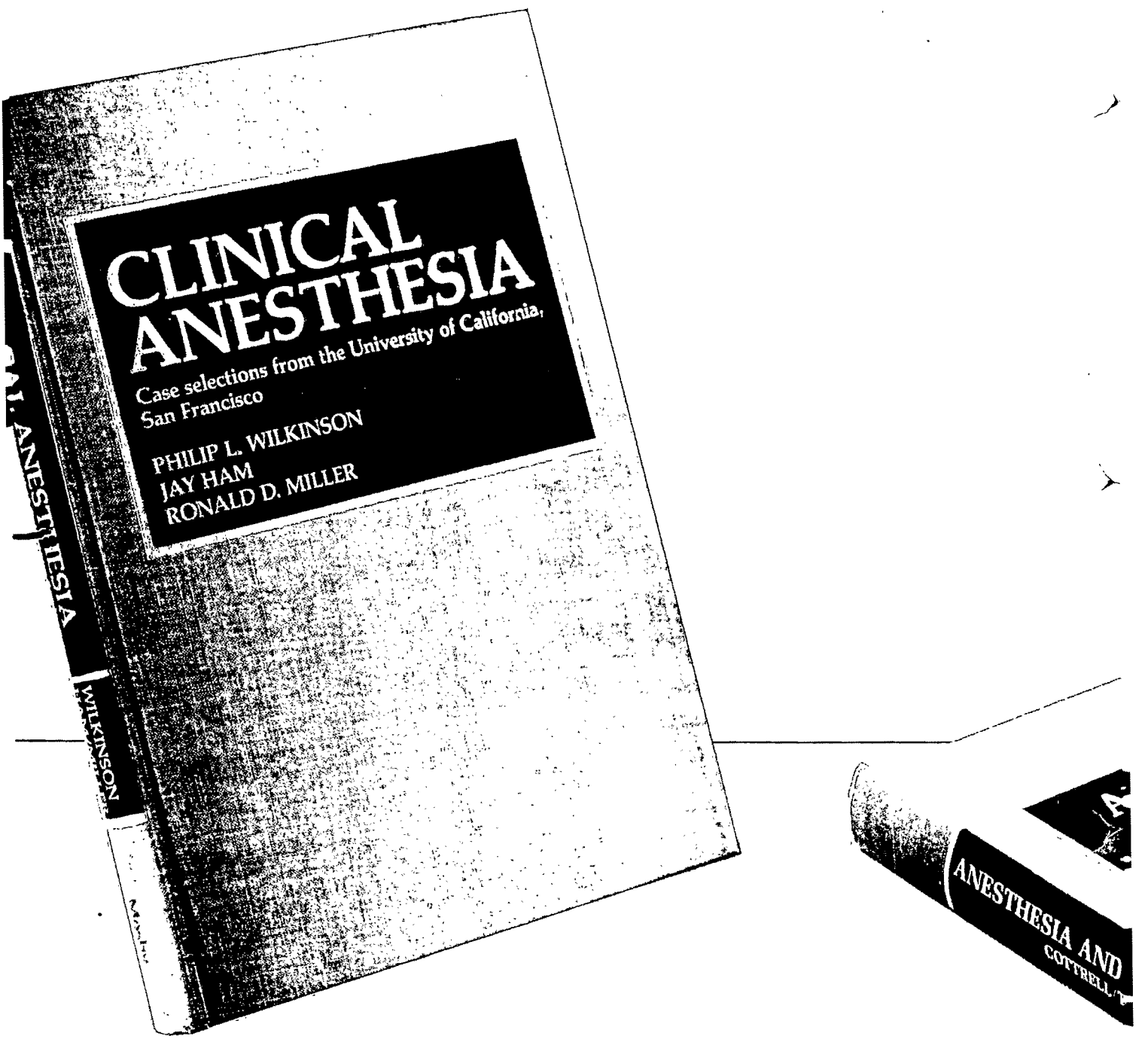
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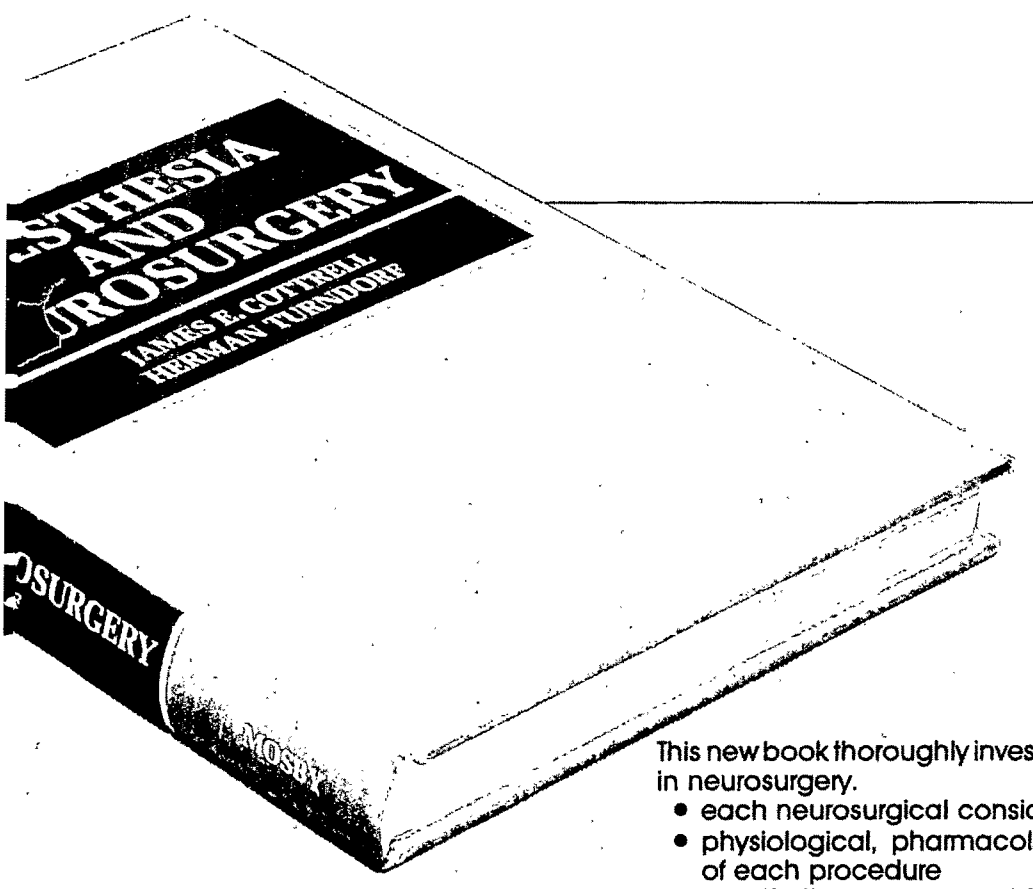
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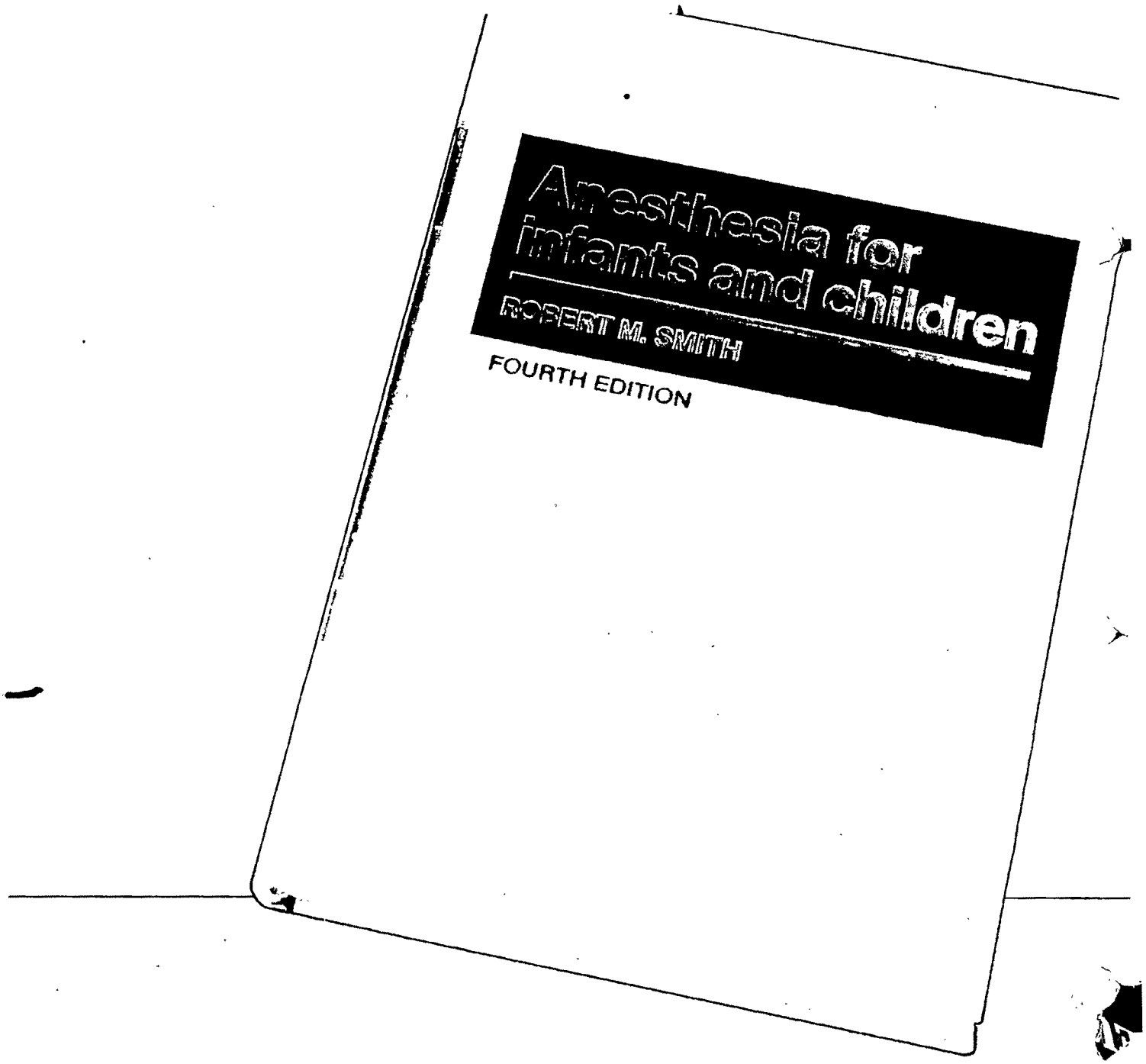
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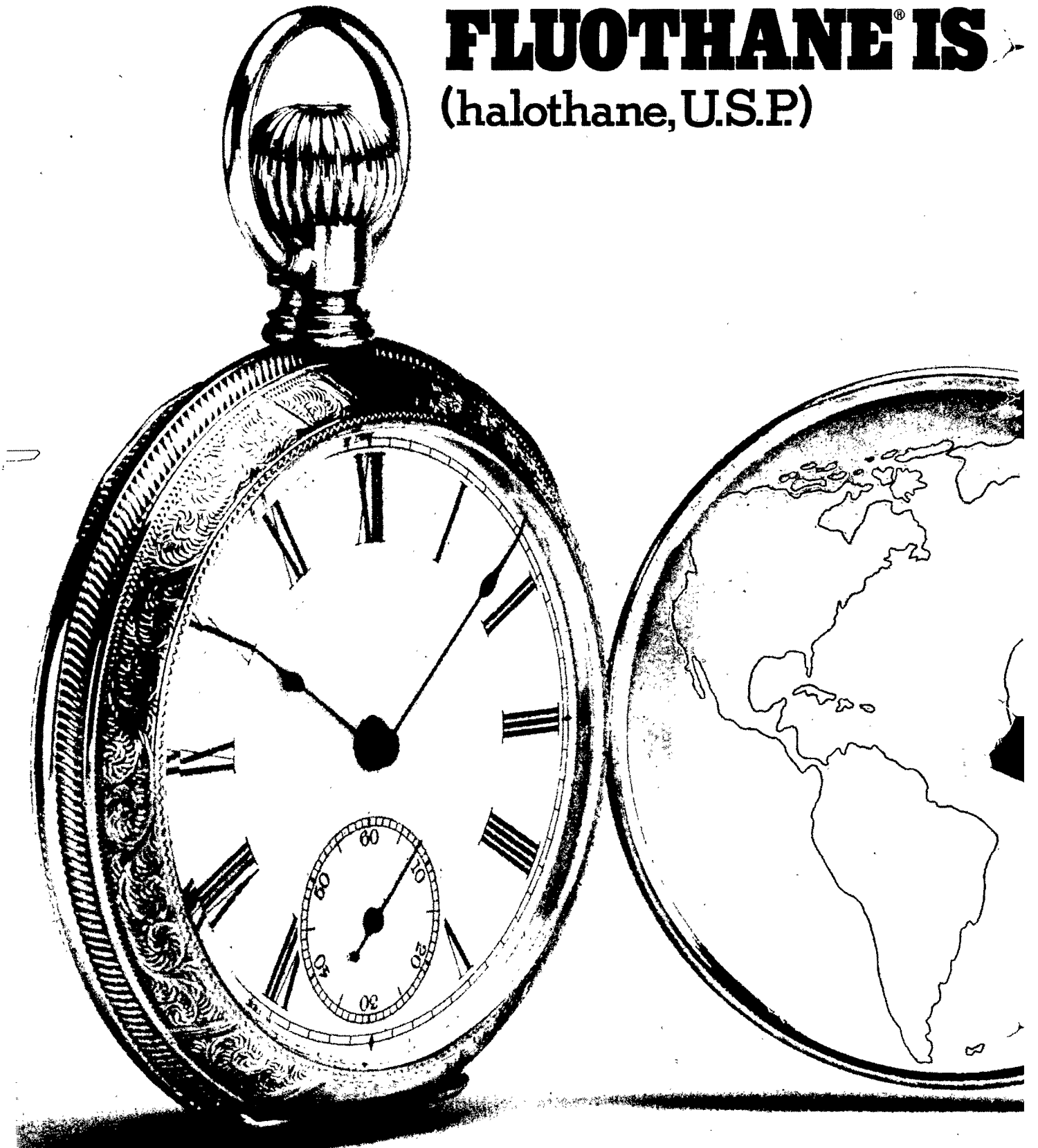
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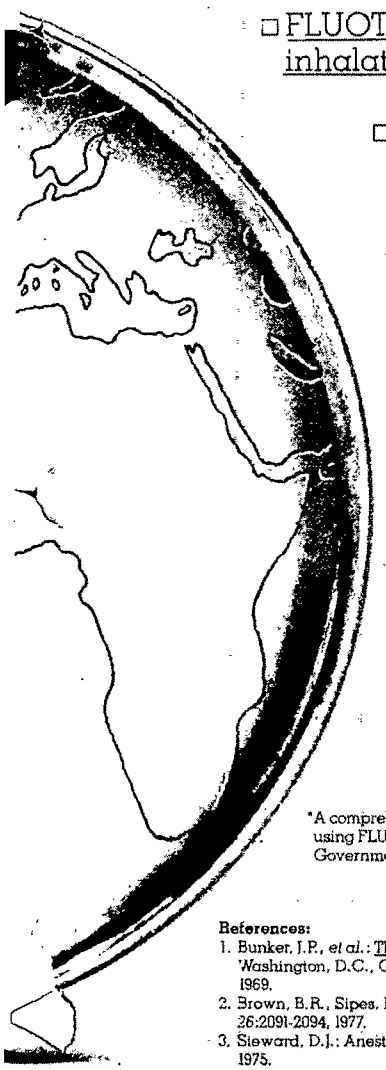
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*A comprehensive retrospective analysis covering 856,000 general anesthesias—nearly one-third using FLUOTHANE. Bunker, J.P., *et al.*: The National Halothane Study. Washington, D.C., Government Printing Office, 1969.

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1. Bunker, J.P., *et al.*: The National Halothane Study. Washington, D.C., Government Printing Office, 1969.
2. Brown, B.R., Sipes, I.G.: Biochem. Pharmacol. 26:2091-2094, 1977.
3. Steward, D.J.: Anesthesiology 43:268-276 (Aug.) 1975.
4. Proceedings, Virginia Society of Anesthesiologists, April 20-22, 1979, Richmond, VA.

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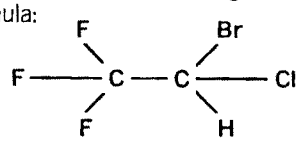
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Description. FLUOTHANE, brand of halothane, U.S.P., is an inhalation anesthetic. It is 2-bromo-2-chloro-1, 1, 1-trifluoroethane and has the following structural formula:



The specific gravity is 1.872-1.877 at 20° C, and the boiling point (range) is 49° C–51° C at 760 mm Hg. The vapor pressure is 243 mm Hg at 20° C. The blood/gas coefficient is 2.5 at 37° C, and the olive oil/water coefficient is 220 at 37° C. Vapor concentrations within anesthetic range are nonirritating and have a pleasant odor. FLUOTHANE is nonflammable, and its vapors mixed with oxygen in proportions from 0.5 to 50 per cent (v/v) are not explosive.

FLUOTHANE does not decompose in contact with warm soda lime. When moisture is present, the vapor attacks aluminum, brass, and lead, but not copper. Rubber, some plastics, and similar materials are soluble in FLUOTHANE; such materials will deteriorate rapidly in contact with FLUOTHANE vapor or liquid. Stability of FLUOTHANE is maintained by the addition of 0.01 per cent thymol (w/w), and storage is in amber colored bottles.

FLUOTHANE should not be kept indefinitely in vaporizer bottles not specifically designed for its use. Thymol does not volatilize along with FLUOTHANE, and therefore accumulates in the vaporizer, and may, in time, impart a yellow color to the remaining liquid or to wicks in vaporizers. The development of such discoloration may be used as an indicator that the vaporizer should be drained and cleaned, and the discolored FLUOTHANE (halothane, U.S.P.) discarded. Accumulation of thymol may be removed by washing with diethyl ether. After cleaning a wick or vaporizer, make certain all the diethyl ether has been removed before reusing the equipment to avoid introducing ether into the system.

Actions. FLUOTHANE is an inhalation anesthetic. Induction and recovery are rapid and depth of anesthesia can be rapidly altered. FLUOTHANE progressively depresses respiration. There may be tachypnea with reduced tidal volume and alveolar ventilation. FLUOTHANE is not an irritant to the respiratory tract, and no increase in salivary or bronchial secretions ordinarily occurs. Pharyngeal and laryngeal reflexes are rapidly obtunded. It causes bronchodilation. Hypoxia, acidosis, or apnea may develop during deep anesthesia.

FLUOTHANE reduces the blood pressure, and frequently decreases the pulse rate. The greater the concentration of the drug, the more evident these changes become. Atropine may reverse the bradycardia. FLUOTHANE does not cause the release of catecholamines from adrenergic stores. FLUOTHANE also causes dilation of the vessels of the skin and skeletal muscles.

Cardiac arrhythmias may occur during FLUOTHANE anesthesia. These include nodal rhythm, AV dissociation, ventricular extrasystoles and asystole. FLUOTHANE sensitizes the myocardial conduction system to the action of epinephrine and norepinephrine, and the combination may cause serious cardiac arrhythmias. FLUOTHANE increases cerebral spinal fluid pressure. FLUOTHANE produces moderate muscular relaxation. Muscle relaxants are used as adjuncts in order to maintain lighter levels of anesthesia. FLUOTHANE augments the action of nondepolarizing relaxants and ganglionic blocking agents. FLUOTHANE is a potent uterine relaxant.

Indications. FLUOTHANE (halothane, U.S.P.) is indicated for the induction and maintenance of general anesthesia.

Contraindications. FLUOTHANE is not recommended for obstetrical anesthesia except when uterine relaxation is required.

Warnings. When previous exposure to FLUOTHANE was followed by unexplained jaundice, consideration should be given to the use of other agents.

FLUOTHANE should be used in vaporizers that permit a reasonable approximation of output, and preferably of the calibrated type. The vaporizer should be placed out of circuit in closed circuit rebreathing systems; otherwise overdosage is difficult to avoid. The patient should be closely observed for signs of overdosage, *i.e.*, depression of blood pressure, pulse rate, and ventilation, particularly during assisted or controlled ventilation.

Usage in Pregnancy. Safe use of FLUOTHANE has not been established with respect to possible adverse effects upon fetal development. Therefore, FLUOTHANE should not be used in women where pregnancy is possible and particularly during early pregnancy, unless, in the judgment of the physician, the potential benefits outweigh the unknown hazards to the fetus.

Precautions. The uterine relaxation obtained with FLUOTHANE, unless carefully controlled, may fail to respond to ergot derivatives and oxytocic posterior pituitary extract.

FLUOTHANE increases cerebrospinal fluid pressure. Therefore, in patients with markedly raised intracranial pressure, if FLUOTHANE is indicated, administration should be preceded by measures ordinarily used to reduce cerebrospinal fluid pressure. Ventilation should be carefully assessed, and it may be necessary to assist or control ventilation to insure adequate oxygenation and carbon dioxide removal.

Epinephrine or norepinephrine should be employed cautiously, if at all, during FLUOTHANE (halothane, U.S.P.) anesthesia since their simultaneous use may induce ventricular tachycardia or fibrillation.

Nondepolarizing relaxants and ganglionic blocking agents should be administered cautiously, since their actions are augmented by FLUOTHANE.

Adverse Reactions. The following adverse reactions have been reported: mild, moderate and severe hepatic dysfunction (including hepatic necrosis), cardiac arrest, hypotension, respiratory arrest, cardiac arrhythmias, hyperpyrexia, shivering, nausea, and emesis.

Dosage and Administration. FLUOTHANE may be administered by the nonrebreathing technic, partial rebreathing, or closed technic. The induction dose varies from patient to patient. The maintenance dose varies from 0.5 per cent to 1.5 per cent.

FLUOTHANE may be administered with either oxygen or a mixture of oxygen and nitrous oxide.

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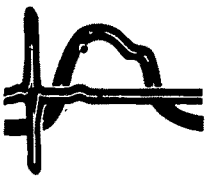
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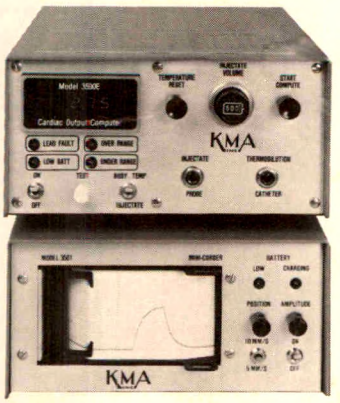
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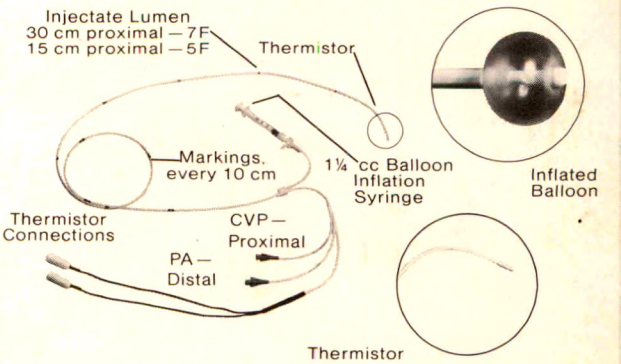
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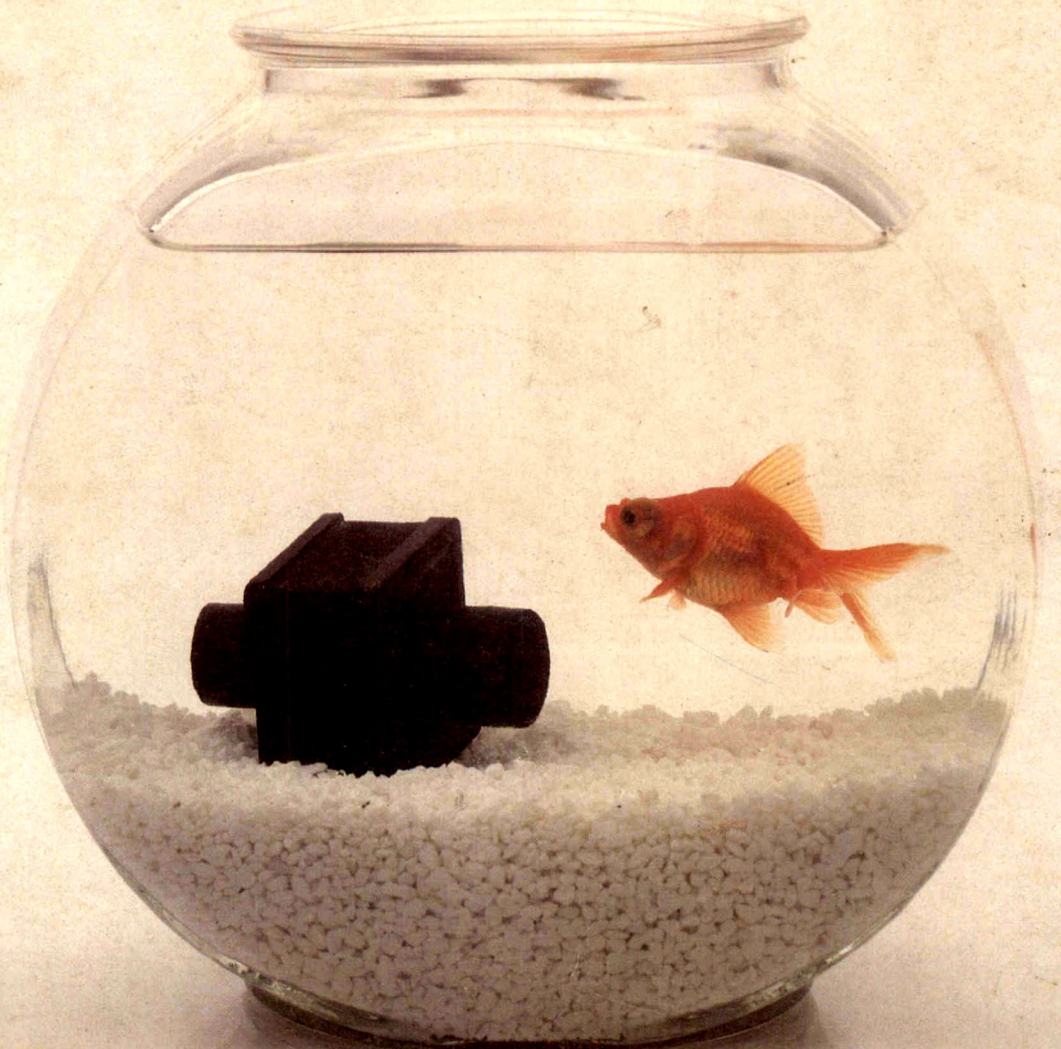
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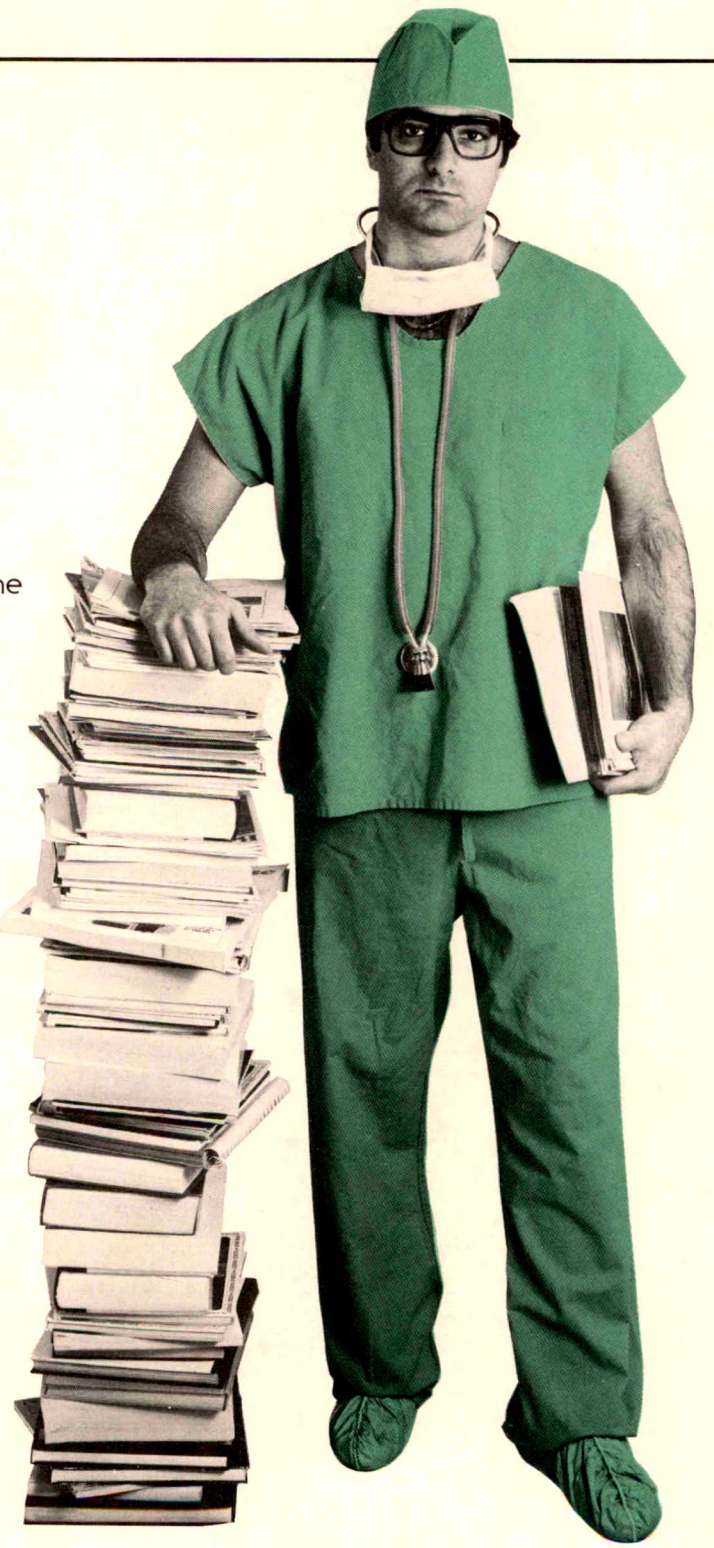
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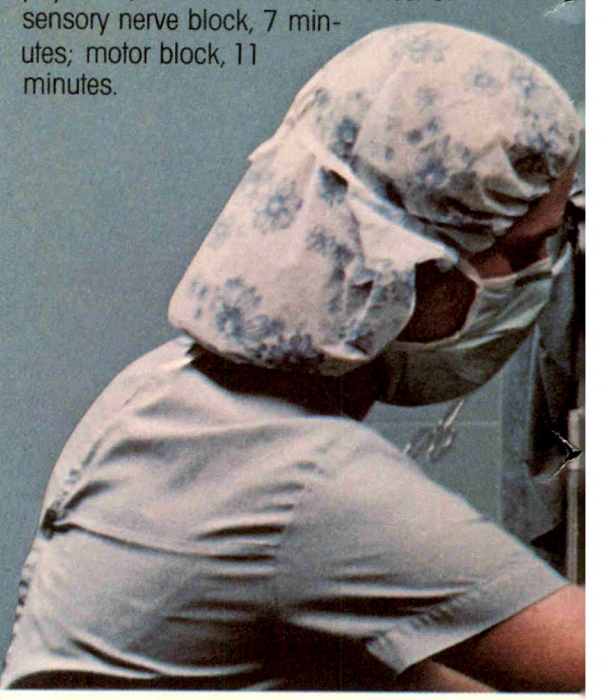
Nesacaine is safe. Rapid hydrolysis by plasma pseudocholinesterase reduces potential risks of systemic toxicity, adverse CNS effects, and cardiovascular problems.[1-4] Half-life in blood is measured in seconds, not hours.

Nesacaine is flexible. Rapid onset and rapid hydrolysis allow quick restoration of normal function. This combination allows easy adjustment of dosage to fit both patient and situation in long, continuous procedures.

Rapid onset allows surgery to begin promptly. Saves time for patient, physician, and nurses. Mean onset of sensory nerve block, 7 minutes; motor block, 11 minutes.

Emergency surgery in more than 500 patients demonstrates rapid onset and minimal side effects.[5]

	SENSORY BLOCK (minutes)		MOTOR BLOCK (minutes)		
	ONSET	DURATION	ONSET	DURATION	SIDE EFFECTS %
chloroprocaine	7	67	11	64	1.3
N	520	154	520	105	



Nesacaine and Nesacaine-CE (chloroprocaine HCl) Injections

Brief Summary:

NESACAINE, in multidose vials with preservative, is indicated for the production of local anesthesia by infiltration and regional nerve block; it should not be used for caudal or epidural anesthesia.

NESACAINE-CE, in single dose vials without preservative, is indicated for the production of local anesthesia by infiltration and regional nerve block, including caudal and epidural blocks.

Contraindications: Hypersensitivity to drugs of the PABA ester group; central nervous system disease is a contraindication to caudal or epidural block.

Warnings: RESUSCITATIVE EQUIPMENT AND DRUGS SHOULD BE IMMEDIATELY AVAILABLE WHEN ANY LOCAL ANESTHETIC IS USED.

Usage in Pregnancy: Safe use of chloroprocaine HCl has not been established with respect to adverse effects upon fetal development. This fact should be carefully considered before administering the drug to women of child-bearing potential, particularly during early pregnancy.

Obstetrical Paracervical Block: Chloroprocaine is not recommended for obstetrical paracervical block when toxemia of pregnancy is present or when fetal distress or prematurity is anticipated in advance of the block. Fetal bradycardia has been noted by electronic monitoring in about 5-10% of the cases where initial doses of 120 mg to 140 mg of chloroprocaine were used. The incidence of bradycardia, within this dose range, might not be dose related. These data are limited and are generally restricted to non-toxemic cases where fetal distress or prematurity was not anticipated in advance of the block. The role of drug factors and non-drug factors associated with fetal bradycardia following paracervical block are unexplained at this time.

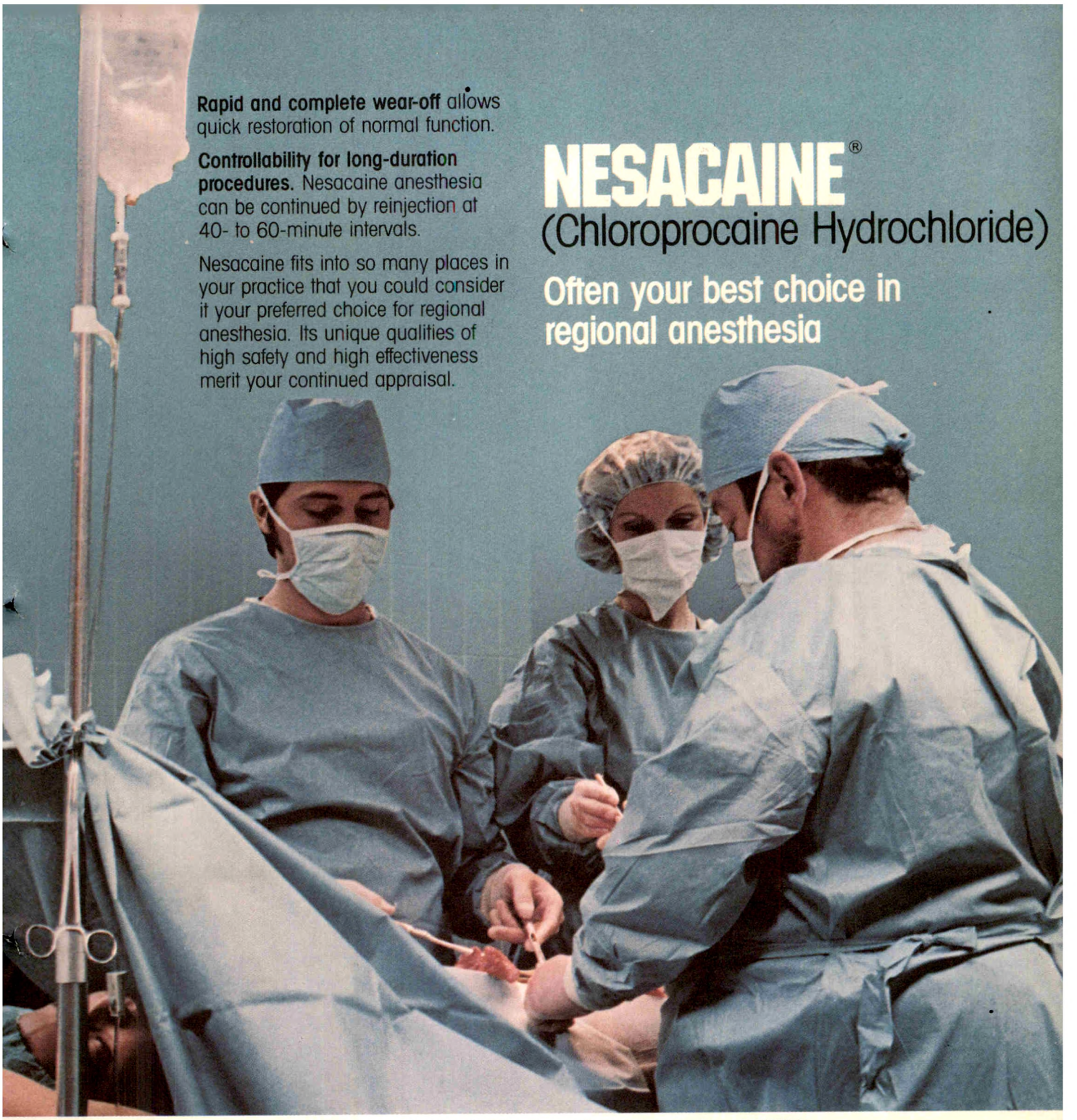
In obstetrics, some oxytocic drugs may cause severe persistent hypertension if vasoconstrictor drugs are used to correct hypotension or are added to the local anesthetic solution.

Solutions containing vasoconstrictors, particularly epinephrine and norepinephrine, should be used with extreme caution in patients receiving MAO inhibitors and tricyclic antidepressants, since severe prolonged hypertension may occur.

Precautions: The safety and effectiveness of chloroprocaine HCl depends upon proper dosage, correct technique, adequate precautions and readiness for emergencies.

Solutions containing vasoconstrictors should be used cautiously in the presence of disease which may adversely affect the patient's cardiovascular system, in areas where the blood supply is limited, or when peripheral vascular disease is present.

Injections should always be made slowly and with frequent aspirations to avoid inadvertent rapid intravascular administration which can produce systemic toxicity.



Rapid and complete wear-off allows quick restoration of normal function.

Controllability for long-duration procedures. Nesacaine anesthesia can be continued by reinjection at 40- to 60-minute intervals.

Nesacaine fits into so many places in your practice that you could consider it your preferred choice for regional anesthesia. Its unique qualities of high safety and high effectiveness merit your continued appraisal.

NESACAINE®
(Chloroprocaine Hydrochloride)

Often your best choice in regional anesthesia

Serious cardiac arrhythmias may occur if preparations containing a vasopressor are used in patients during or following the administration of chloroform, halothane, cyclopropane, trichloroethylene, or other related agents.

Adverse Reactions: Systemic adverse reactions result from high plasma levels due to rapid absorption, inadvertent intravascular injection, excessive dosage, hypersensitivity, idiosyncrasy, or diminished tolerance.

Central nervous system reactions: Excitation and/or depression; restlessness, anxiety, dizziness, blurred vision, or tremors, possibly proceeding to convulsions. Depression may be the first manifestation followed by drowsiness merging into unconsciousness and respiratory arrest.

Cardiovascular system reactions: Depression of the myocardium manifested by an initial episode of hypotension, bradycardia, and cardiac arrest.

Neurologic adverse reactions: In the practice of epidural block, occasional inadvertent penetration of the subarachnoid space may occur; subsequent reactions may include spinal block of varying magnitude, loss of bowel and bladder control, loss of perineal sensation and sexual function. Persistent neurological deficit of some lower spinal segments with slow recovery (several months) has been reported in rare instances.

Dosage and Administration: See full prescribing information.

NESACAINE is supplied in 1% and 2% solutions in 30 ml multiple dose vials.

NESACAINE-CE is supplied in 2% and 3% solutions in 30 ml single dose vials.

REFERENCES:

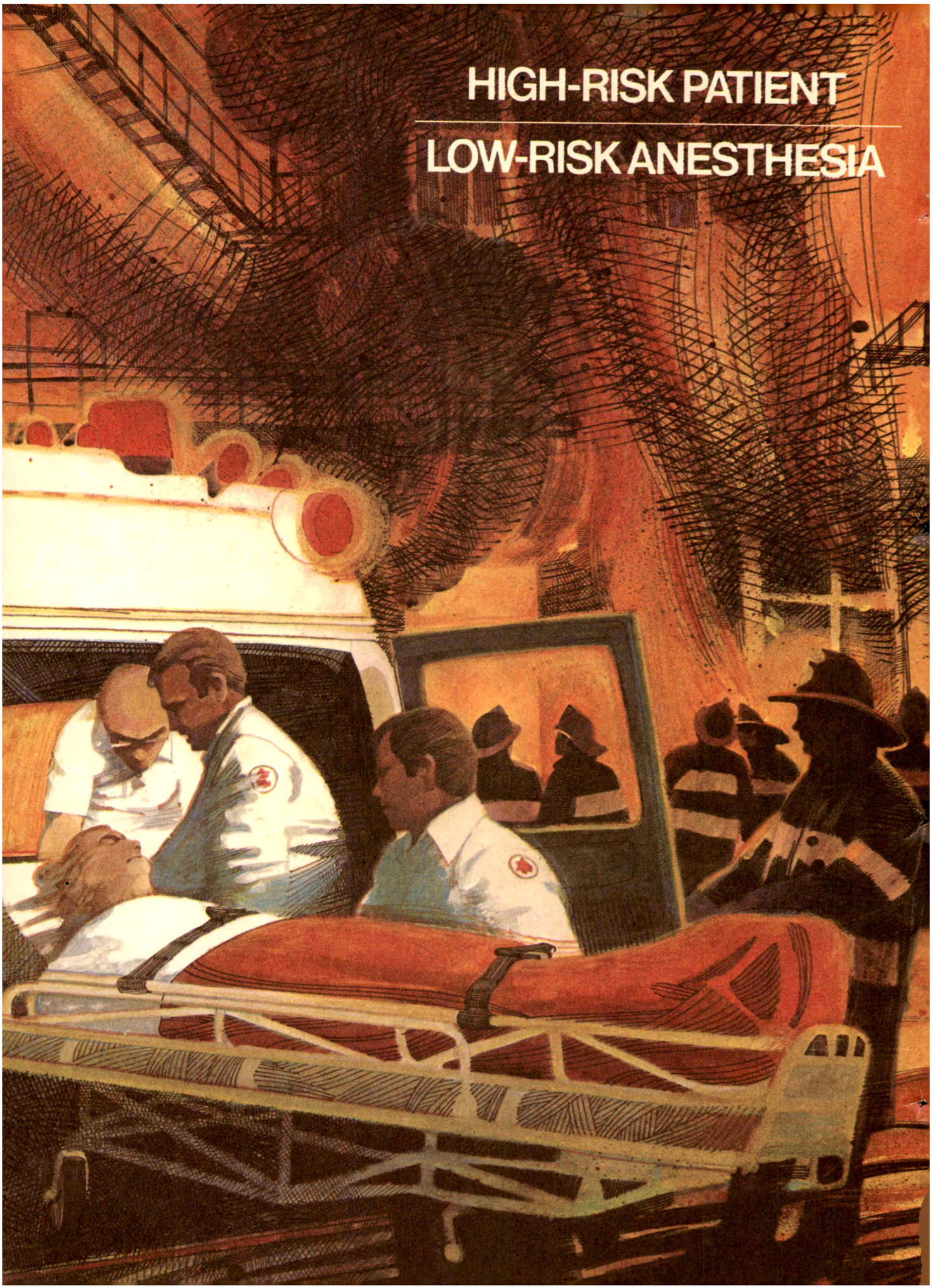
1. Bonica JJ (ed): Obstetric Analgesia and Anesthesia. Berlin, Heidelberg, Springer-Verlag, 1972, pp 19, 51-52.
2. Nesacaine® (chloroprocaine hydrochloride) in obstetrical and surgical regional anesthesia. a Symposium, New York, KPR Infor/Media Corp, 1977, pp 12-27.
3. Ansbro FP, Blundell AE, Furlong RE, et al: Chloroprocaine (Nesacaine): Its relative nontoxicity as demonstrated by epidural anesthesia. Arch Surg 78:75-78, 1959.
4. Foldes FF: The management of pain in ambulatory patients. Med Science Donat 7:26-37, 1969. (Proceedings of Symposium on Pain, Amsterdam, March 1, 1969.)
5. Zsigmond EK, Kothary SP: 2-Chloroprocaine: Clinical pharmacology, pharmacokinetics and its safety in regional anesthesia. Presented as a scientific exhibit at the International Anesthesia Research Society, Hollywood, Fla, March 11-15, 1979.

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ROCHESTER, NEW YORK 14623

A268


HIGH-RISK PATIENT
LOW-RISK ANESTHESIA

Ketalar®
(ketamine hydrochloride injection, NF)

Features you need...

Smooth, rapid onset of anesthesia, profound analgesia, IM or IV administration. Little risk of liver damage or buildup of tolerance following repeated procedures. Ketalar usually strengthens, rather than depresses, blood pressure, pulse rate and respiration. When necessary, it permits maintenance of unaided respiration because of minimal relaxation of skeletal muscles or laryngeal-pharyngeal reflexes.

for the patients who need them

At either end of the age spectrum, the pediatric or geriatric patient. The patient in shock, or with shock potential. Patients in whom establishing an IV route of administration is difficult. The burn patient requiring repeated dressing changes. Patients requiring manipulative or diagnostic procedures. The debilitated patient. The emergency patient who may not have an empty stomach.

BRIEF SUMMARY OF PRESCRIBING INFORMATION.

SPECIAL NOTE

EMERGENCE REACTIONS HAVE OCCURRED IN APPROXIMATELY 12% OF PATIENTS.

THE PSYCHOLOGICAL MANIFESTATIONS VARY IN SEVERITY BETWEEN PLEASANT, DREAMLIKE STATES, VIVID IMAGERY, HALLUCINATIONS, AND EMERGENCE DELIRIUM. IN SOME CASES, THESE STATES HAVE BEEN ACCOMPANIED BY CONFUSION, EXCITEMENT, AND IRRATIONAL BEHAVIOR WHICH A FEW PATIENTS RECALL AS AN UNPLEASANT EXPERIENCE. THE DURATION ORDINARILY LASTS NO MORE THAN A FEW HOURS; IN A FEW CASES, HOWEVER, RECURRENCES HAVE TAKEN PLACE UP TO 24 HOURS POSTOPERATIVELY. NO RESIDUAL PSYCHOLOGICAL EFFECTS ARE KNOWN TO HAVE RESULTED FROM USE OF KETALAR.

THE INCIDENCE OF THESE EMERGENCE PHENOMENA IS LEAST IN THE YOUNG (15 YEARS OF AGE OR LESS) AND ELDERLY (OVER 65 YEARS OF AGE) PATIENT. ALSO, THEY ARE LESS FREQUENT WHEN THE DRUG IS GIVEN INTRAMUSCULARLY.

THESE REACTIONS MAY BE REDUCED IF VERBAL, TACTILE, AND VISUAL STIMULATION OF THE PATIENT IS MINIMIZED DURING THE RECOVERY PERIOD. THIS DOES NOT PRECLUDE THE MONITORING OF VITAL SIGNS. IN ADDITION, THE USE OF A SMALL HYPNOTIC DOSE OF A SHORT-ACTING OR ULTRA-SHORT-ACTING BARBITURATE MAY BE REQUIRED TO TERMINATE A SEVERE EMERGENCE REACTION. THE INCIDENCE OF EMERGENCE REACTIONS IS REDUCED AS EXPERIENCE WITH THE DRUG IS GAINED.

WHEN KETALAR IS USED ON AN OUTPATIENT BASIS, THE PATIENT SHOULD NOT BE RELEASED UNTIL RECOVERY FROM ANESTHESIA IS COMPLETE AND THEN SHOULD BE ACCOMPANIED BY A RESPONSIBLE ADULT.

CONTRAINDICATIONS

Ketamine hydrochloride is contraindicated in those in whom a significant elevation of blood pressure would constitute a serious hazard and those who have shown hypersensitivity to the drug.

WARNINGS

1. Ketalar should be used by or under the direction of physicians experienced in administering general anesthetics and in maintenance of an airway and in the control of respiration.
2. Cardiac function should be continually monitored during the procedure in patients found to have hypertension or cardiac decompensation.
3. Barbiturates and Ketalar, being chemcially incompatible because of precipitate formation, *should not* be injected from the same syringe.
4. Prolonged recovery time may occur if barbiturates and/or narcotics are used concurrently with Ketalar.
5. Postoperative confusional states may occur during the recovery period.
6. Respiratory depression may occur with overdosage or too rapid a rate of administration of Ketalar, in which case supportive ventilation should be employed. Mechanical support of respiration is preferred to administration of analeptics.

Usage in Pregnancy: Since the safe use in pregnancy, including obstetrics (either vaginal or abdominal delivery), has not been established, such use is not recommended.

PRECAUTIONS

1. Because pharyngeal and laryngeal reflexes are usually active, Ketalar (ketamine HCl injection) should not be used alone in surgery or diagnostic procedures of the pharynx, larynx, or bronchial tree. Mechanical stimulation of the pharynx should be avoided, whenever possible, if Ketalar is used alone. Muscle relaxants, with proper attention to respiration, may be required in both of these instances.
2. Resuscitative equipment should be ready for use.
3. **The incidence of emergence reactions may be reduced** if verbal and tactile stimulation of the patient is minimized during the recovery period. This does not preclude the monitoring of vital signs (see Special Note).
4. The intravenous dose should be administered over a period of 60 seconds. More rapid administration may result in respiratory depression or apnea and enhanced pressor response.
5. In surgical procedures involving visceral pain pathways, Ketalar should be supplemented with an agent which obtunds visceral pain.
6. Use with caution in the chronic alcoholic and the acutely alcohol-intoxicated patient.
7. An increase in cerebrospinal fluid pressure has been reported following administration of ketamine hydrochloride. Use with extreme caution in patients with preanesthetic elevated cerebrospinal fluid pressure.

ADVERSE REACTIONS

Cardiovascular: Blood pressure and pulse rate are frequently elevated following administration of Ketalar. However, hypotension and bradycardia have been observed. Arrhythmia has also occurred.

Respiration: Although respiration is frequently stimulated, severe depression of respiration or apnea may occur following rapid intravenous administration of high doses of Ketalar (ketamine HCl injection). Laryngospasms and other forms of airway obstruction have occurred during Ketalar anesthesia.

Eye: Diplopia and nystagmus have been noted following Ketalar administration. It also may cause a slight elevation in intraocular pressure measurement.

Psychological: (See Special Note).

Neurological: In some patients, enhanced skeletal muscle tone may be manifested by tonic and clonic movements sometimes resembling seizures (see Dosage and Administration).

Gastrointestinal: Anorexia, nausea and vomiting have been observed; however this is not usually severe and allows the great majority of patients to take liquids by mouth shortly after regaining consciousness (see Dosage and Administration).

General: Local pain and exanthema at the injection site have infrequently been reported. Transient erythema and/or morbilliform rash have also been reported.

HOW SUPPLIED

Ketalar is supplied as the hydrochloride in concentrations equivalent to ketamine base.

N 0071-4581-15—Each 50-ml vial contains 10 mg/ml. Supplied in cartons of 10.
N 0071-4581-12—Each 20-ml vial contains 10 mg/ml. Supplied in cartons of 10.
N 0071-4582-10—Each 10-ml vial contains 50 mg/ml. Supplied in cartons of 10.
N 0071-4585-08—Each 5-ml vial contains 100 mg/ml. Supplied in cartons of 10.

SG

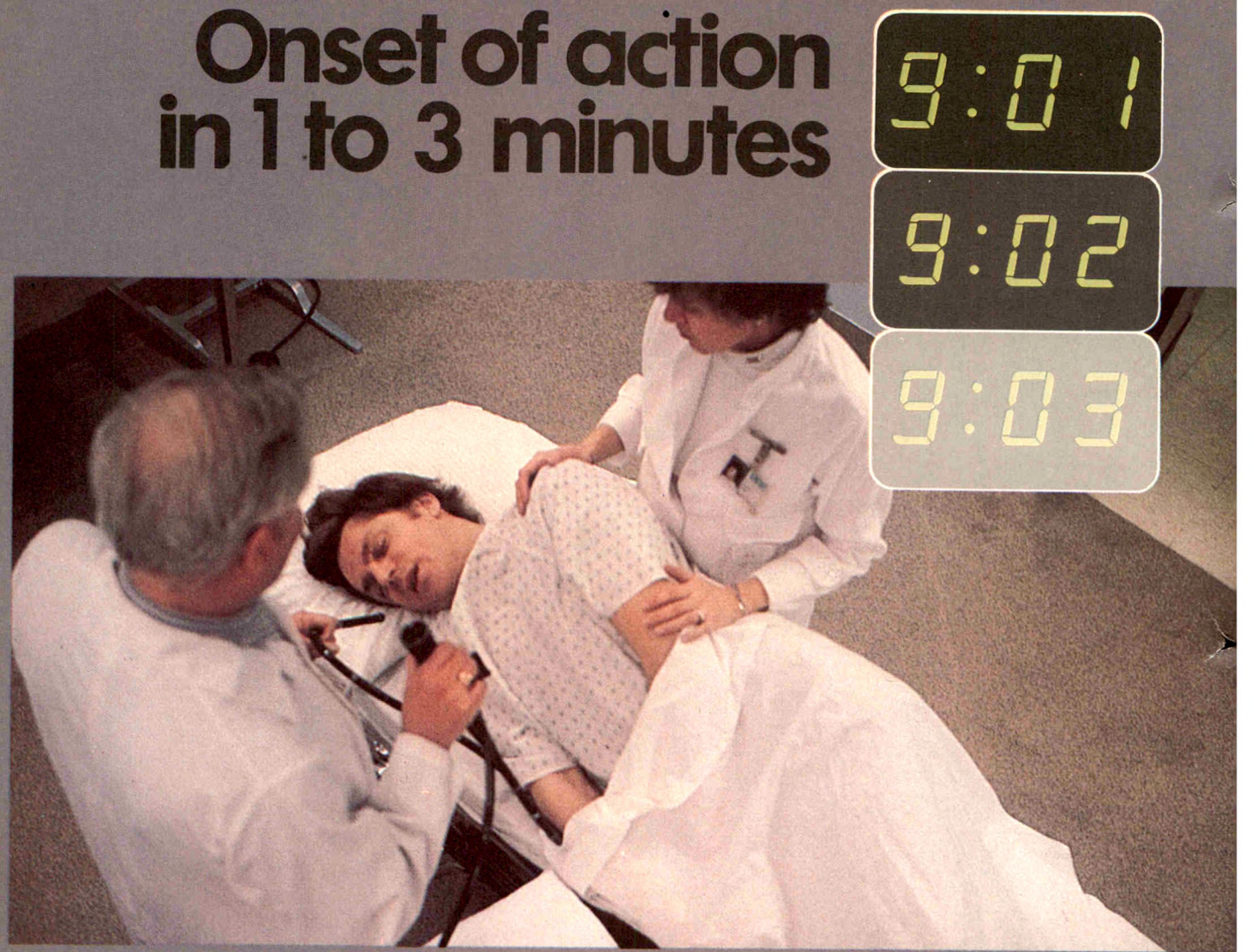
PARKE-DAVIS

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PARKE-DAVIS
Division of Warner-Lambert Company
Morris Plains, NJ 07950

Onset of action in 1 to 3 minutes



for a calmer, relaxed patient

When impending surgery causes high levels of anxiety, administering Valium (diazepam/Roche) I.V. can be a valuable pre-anesthetic maneuver. Within 3 minutes, Injectable Valium reaches peak blood levels, promptly relieving patients of excessive apprehension.

Diminished recall

Within three minutes of injection, Valium I.V. produces anterograde amnesia. This important property allows most patients to virtually forget induction of anesthesia, passage of endoscopic instruments and similar distressing events. However, when required, patients usually can respond to directions—an important advantage in surgery conducted under regional anesthesia or in procedures such as endoscopy and cardioversion.

Permits reduction of analgesic dosage

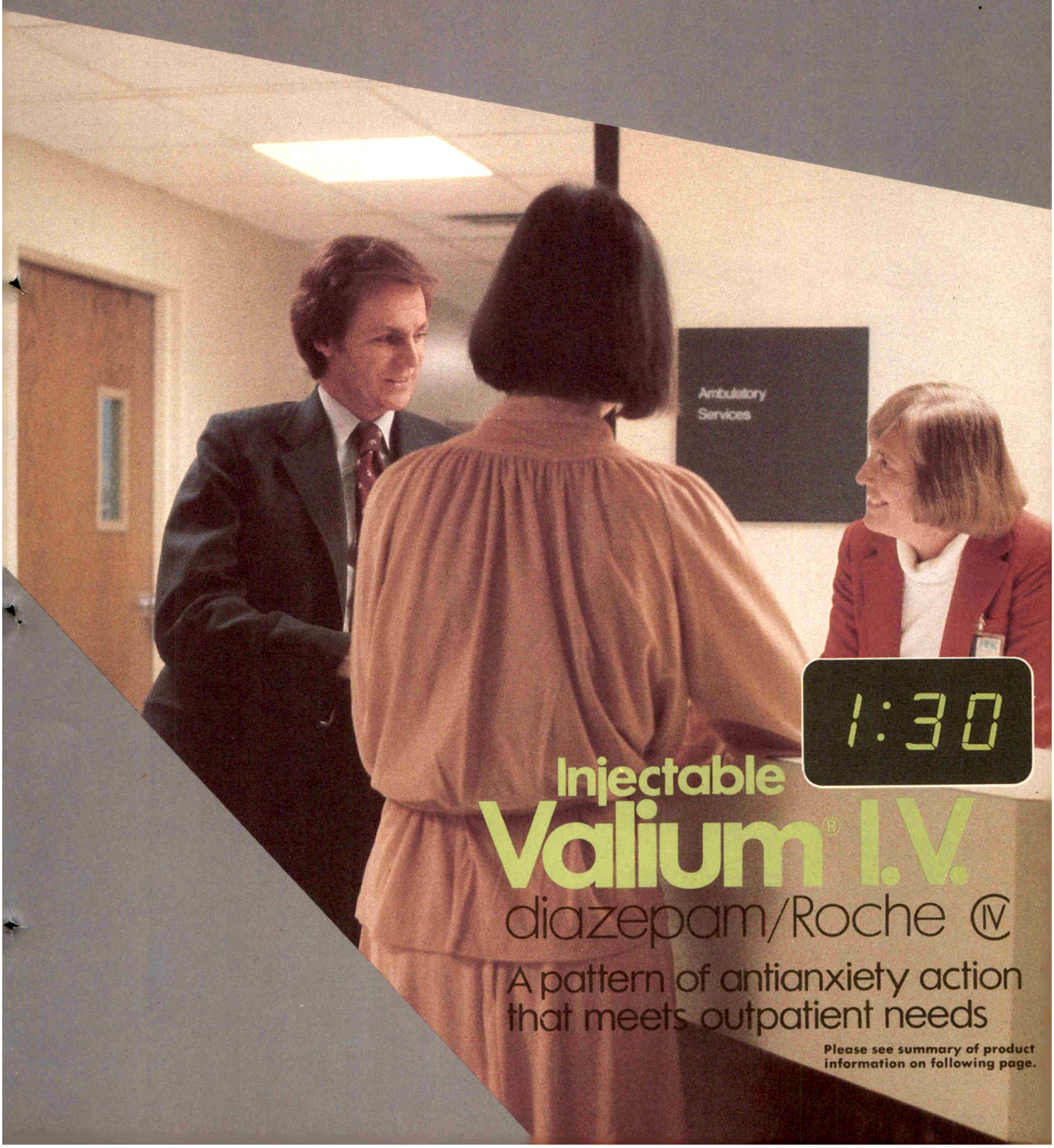
When Valium I.V. is used with a narcotic analgesic, the dosage of the narcotic can and should be reduced by at least one-third. In some cases the use of a narcotic may not be necessary.

Predictable duration of action

Because the sedating effect of Valium (diazepam/Roche) I.V. is of predictable duration, patients can be released only a few hours after minor surgery or short-term diagnostic procedures. By then, alertness is restored, since post-procedural drowsiness is minimal and short-lived. As with most CNS-acting drugs, patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness, such as operating machinery or driving.

ROCHE®

Hours later ready to be released



Injectable Valium® I.V.

diazepam/Roche (IV)

A pattern of antianxiety action that meets outpatient needs

Please see summary of product information on following page.

Improved Tel-E-Ject®

10-mg Disposable Syringe (5 mg/ml)

scale on both sides of barrel eases visibility during administration





Injectable Valium® I.V.

diazepam/Roche

10-ml vials
2-ml ampuls } 5 mg/ml

Please consult complete product information, a summary of which follows:

Contraindications: Hypersensitivity; acute narrow angle glaucoma; may be used in patients with open angle glaucoma receiving appropriate therapy.

Warnings: *To reduce the possibility of venous thrombosis, phlebitis, local irritation, swelling, and, rarely, vascular impairment when used I.V.: inject slowly, taking at least one minute for each 5 mg (1 ml) given; do not use small veins, i.e., dorsum of hand or wrist; use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute Valium (diazepam/Roche) with other solutions or drugs in syringe or infusion flask. If it is not feasible to administer Valium directly I.V., it may be injected slowly through the infusion tubing as close as possible to the vein insertion.*

Administer with extreme care to elderly, very ill, those with limited pulmonary reserve because of possibility of apnea and/or cardiac arrest; concomitant use of barbiturates, alcohol or other CNS depressants increases depression with increased risk of apnea; have resuscitative facilities available. When used with narcotic analgesic, eliminate or reduce narcotic dosage at least ⅓, administer in small increments. Should not be administered to patients in shock, coma, acute alcoholic intoxication with depression of vital signs. As with most CNS-acting drugs, caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).

Has precipitated tonic status epilepticus in patients treated for petit mal status or petit mal variant status.

Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation after long use of excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after long, continuous use at high therapeutic levels. After extended therapy, gradually taper dosage.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations, as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Not recommended for OB use.

Efficacy/safety not established in neonates (age 30 days or less); prolonged CNS depression observed. In children, give slowly (up to 0.25 mg/kg over 3 minutes) to avoid apnea or prolonged somnolence; can be repeated after 15 to 30 minutes. If no relief after third administration, appropriate adjunctive therapy is recommended.

Precautions: Although promptly controlled, seizures may return; re-administer if necessary; not recommended for long-term maintenance therapy. If combined with other psychotropics or anticonvulsants, carefully consider individual pharmacologic effects—particularly with known compounds which may potentiate action of Valium (diazepam/Roche), *i.e.*, phenothiazines, narcotics, barbiturates, MAO inhibitors, antidepressants. Protective measures indicated in highly anxious patients with accompanying depression who may have suicidal tendencies. Observe usual precautions in impaired hepatic function; avoid accumulation in patients with compromised kidney function. Laryngospasm/increased cough reflex are possible during peroral endoscopic procedures; use topical anesthetic, have necessary countermeasures available. Hypotension or muscular weakness possible, particularly when used with narcotics, barbiturates or alcohol. Use lower doses (2 to 5 mg) for elderly/debilitated.

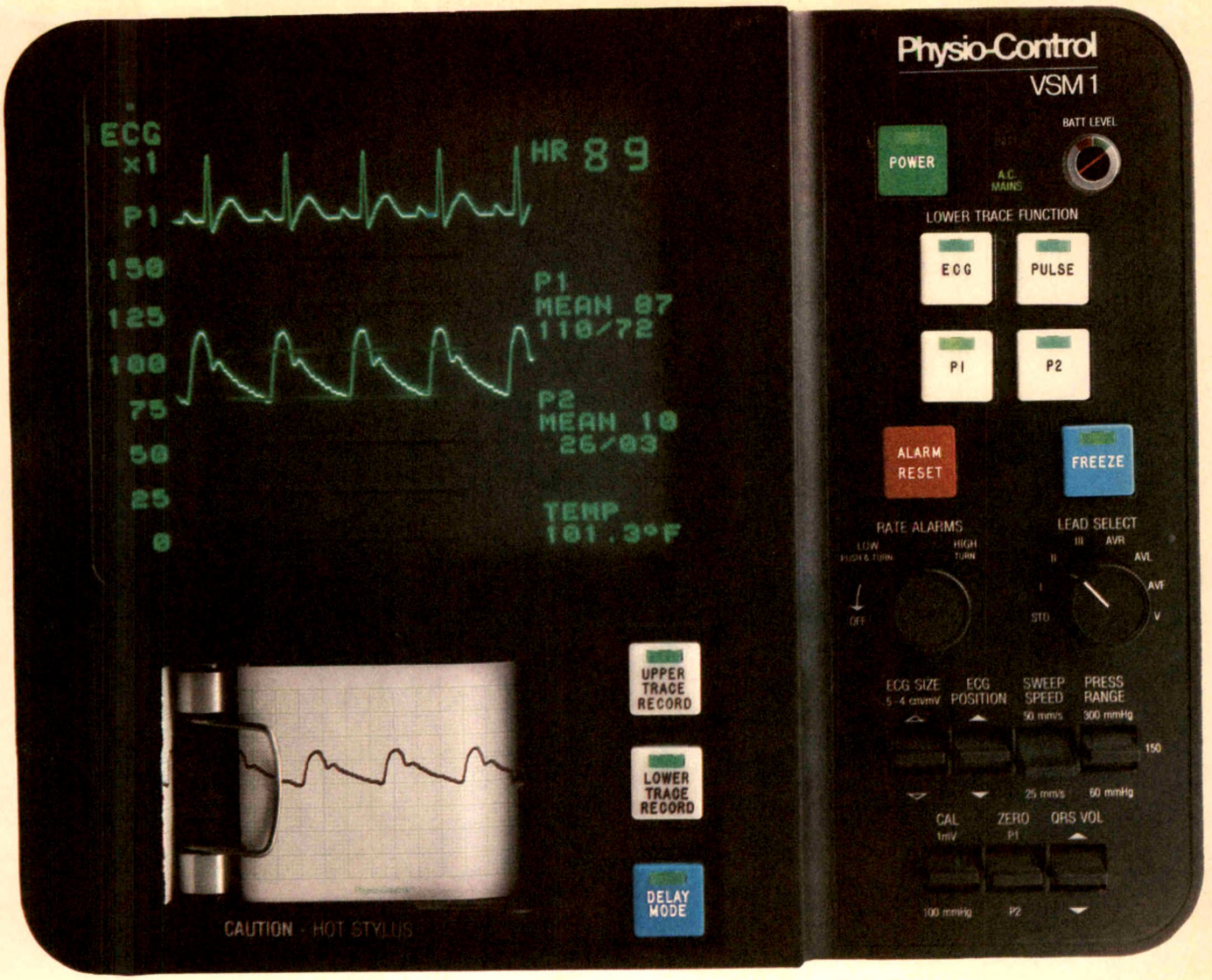
Adverse Reactions: Drowsiness, fatigue, ataxia, venous thrombosis/phlebitis at injection site, confusion, depression, dysarthria, headache, hypoactivity, slurred speech, syncope, tremor, vertigo, constipation, nausea, incontinence, changes in libido, urinary retention, bradycardia, cardiovascular collapse, hypotension, blurred vision, diplopia, nystagmus, urticaria, skin rash, hiccups, changes in salivation, neutropenia, jaundice. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Cough, depressed respiration, dyspnea, hyperventilation, laryngospasm/pain in throat and chest have been reported in peroral endoscopic procedures. Isolated reports of neutropenia, jaundice; periodic blood counts, liver function tests advisable during long-term therapy. Minor EEG changes, usually low-voltage fast activity, of no known significance.

Management of Overdosage: Manifestations include somnolence, confusion, coma, diminished reflexes. Monitor respiration, pulse, blood pressure; employ general supportive measures, I.V. fluids, adequate airway. Hypotension may be combated by the use of levarterenol or metaraminol. Dialysis is of limited value.

Supplied: Ampuls, 2 ml, boxes of 10; Vials, 10 ml, boxes of 1; Tel-E-Ject® (disposable syringes), 2 ml, boxes of 10. Each ml contains 5 mg diazepam compounded with 40% propylene glycol, 10% ethyl alcohol, 5% sodium benzoate and benzoic acid as buffers, and 1.5% benzyl alcohol as preservative.

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ROCHE LABORATORIES
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110



Vital signs much improved.

Presenting the all-new VSM-1 vital signs monitor from Physio-Control—conceived, designed and built to do a clearly superior job of physiological monitoring.

The VSM-1 provides continuous display of systolic, diastolic and mean blood pressures for two invasive lines. Pressure zeroing is automatic and pressure scales can be varied throughout three ranges to maximize the size of the pressure wave form display. And you can freeze or record ECG, pulse or either of the two pressures. Temperature, 12 lead ECG, and non-fade trace are also provided.

For all its sophistication, the microprocessor-based VSM-1 is remarkably simple to operate. The instrument is a single compact unit, complete with recorder and a powerful integral battery for portable or emergency operation. Data presentation is clean, crisp and clear. Controls are color-coded by function and grouped logically for ease of operation. A single connector serves for interface with either a defibrillator or remote display.

We should also like to emphasize that the VSM-1 has been designed and engineered to the highest possible standards of reliability. It has been subjected to extensive clinical testing and analysis, including accelerated life tests and reliability demonstration testing. All critical components are preconditioned and rigorously tested.

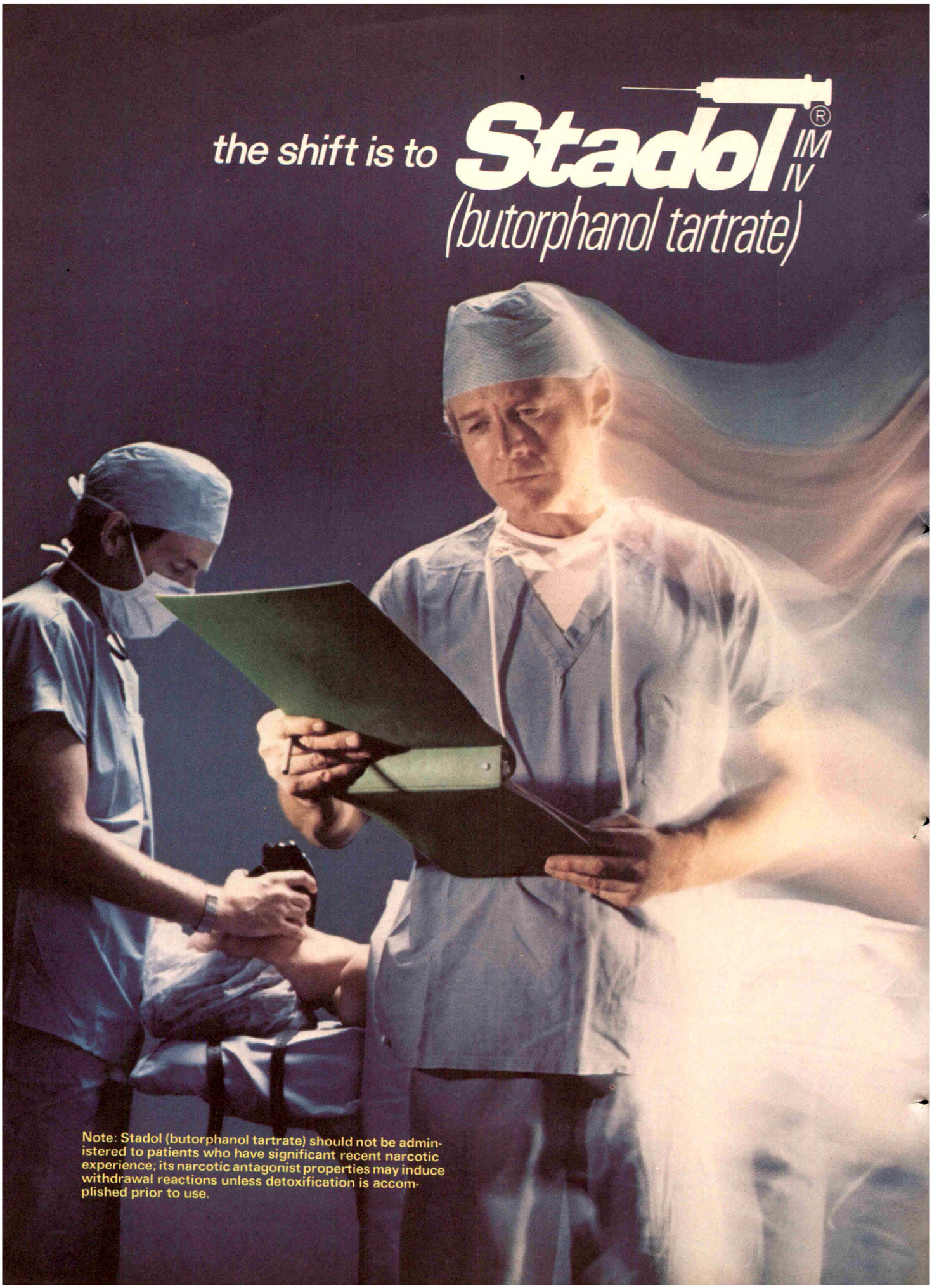
Wherever the VSM-1 is used—OR, CCU, ICU—you can depend on this versatile instrument to turn in an outstanding performance. And like all Physio-Control products, the VSM-1 is backed by the largest, best trained and most dedicated service team in our industry.

Questions? A demonstration? We'd be delighted.

PHYSIO-CONTROL—Manufacturers of the Lifepak® acute cardiac care systems. 11811 Willows Road, Redmond, Washington 98052 USA (206) 881-4000.

Only **Physio-Control** makes the VSM™ 1




the shift is to Stadol® IM IV
(butorphanol tartrate)
Note: Stadol (butorphanol tartrate) should not be administered to patients who have significant recent narcotic experience; its narcotic antagonist properties may induce withdrawal reactions unless detoxification is accomplished prior to use.


for pain management
preoperatively
intraoperatively
postoperatively
in surgery
■ proven analgesic efficacy—as a pre- and postoperative agent...for patients in labor... as the analgesic component of balanced anesthesia
■ fast acting—onset of action within 10 minutes IM, very rapidly IV; peak analgesic activity within 30-60 minutes IM, more rapidly IV
■ limited respiratory depressant potential—2 mg of Stadol produces a degree of respiratory depression similar to that of 10 mg of morphine or 70 mg of meperidine—unlike these agents, doubling the Stadol dose to 4 mg does not appreciably increase the magnitude of respiratory depression
■ favorable side effect profile—low physical dependence liability, little nausea or vomiting, infrequent constipation
■ few CNS effects other than sedation—the reported incidence of euphoria and hallucinations is less than 1%
■ nonscheduled—not subject to regulations under the Federal Controlled Substances Act
Stadol® IM IV
(butorphanol tartrate)
proven performance in the relief of moderate to severe pain
BRISTOL™
Bristol Laboratories
Division of Bristol-Myers Company
Syracuse, New York 13201
Please see brief summary of prescribing information on the following page.
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Brief Summary of Prescribing Information
STADOL® (butorphanol tartrate)

For complete information, consult Official Package Circular.

(2) 12/10/79

INDICATIONS AND USAGE—Stadol is recommended for the relief of moderate to severe pain. Stadol can also be used for preoperative or preanesthetic medication, as a supplement to balanced anesthesia, and for the relief of prepartum pain.

CONTRAINDICATIONS—Stadol should not be administered to patients who have been shown to be hypersensitive to it.

WARNINGS—Patients Physically Dependent on Narcotics: Because of its antagonist properties, Stadol is not recommended for patients physically dependent on narcotics. Detoxification in such patients is required prior to use.
Due to the difficulty in assessing addiction in patients who have recently received substantial amounts of narcotic medication, caution should be used in the administration of Stadol. Detoxification of such patients prior to usage should be carefully considered.

Drug Dependence: Special care should be exercised in administering Stadol to emotionally unstable patients and to those with a history of drug misuse. When long-term therapy is contemplated, such patients should be closely supervised. Even though Stadol has a low physical dependence liability, care should be taken that individuals who may be prone to drug abuse are closely supervised. It is important to avoid increases in dose and frequency of injections by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

Head Injury and Increased Intracranial Pressure: Although there is no clinical experience in patients with head injury, it can be assumed that Stadol, like other potent analgesics, elevates cerebrospinal fluid pressure. Therefore the use of Stadol in cases of head injury can produce effects (e.g., miosis) which may obscure the clinical course of patients with head injuries. In such patients Stadol must be used with extreme caution and only if its use is deemed essential.

Cardiovascular Effects: Because Stadol increases the work of the heart, especially the pulmonary circuit, the use of this drug in acute myocardial infarction or in cardiac patients with ventricular dysfunction or coronary insufficiency should be limited to those who are hypersensitive to morphine sulfate or meperidine.

PRECAUTIONS—Certain Respiratory Conditions: Because Stadol causes some respiratory depression, it should be administered only with caution and low dosage to patients with respiratory depression (e.g., from other medication, uremia, or severe infection), severely limited respiratory reserve, bronchial asthma, obstructive respiratory conditions, or cyanosis.

Impaired Renal or Hepatic Function: Although laboratory tests have not indicated that Stadol causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Extensive liver disease may predispose to greater side effects and greater activity from the usual clinical dose, possibly the result of decreased metabolism of the drug by the liver.

Biliary Surgery: Clinical studies have not been done to establish the safety of Stadol administration to patients about to undergo surgery of the biliary tract.

Usage as a Preoperative or Preanesthetic Medication: Slight increases in systolic blood pressure may occur, therefore caution should be employed when Stadol is used in the hypertensive patient.

Usage in Balanced Anesthesia: The use of pancuronium in combination with Stadol may cause an increase in conjunctival changes.

Usage in Pregnancy: The safety of Stadol for use in pregnancy prior to the labor period has not been established; therefore, this drug should be used in pregnant patients only when in the judgment of the physician its use is deemed essential to the welfare of the patient.

Reproduction studies have been performed in rats, mice and rabbits and have revealed no evidence of impaired fertility or harm to the fetus due to Stadol at about 2.5 to 5 times the human dose.

Usage in Labor and Delivery: Safety to the mother and fetus following administration of Stadol during labor has been established. Patients receiving Stadol during labor have experienced no adverse effects other than those observed with commonly used analgesics. Stadol should be used with caution in women delivering premature infants.

Usage in Nursing Mothers: The use of Stadol in lactating mothers who are nursing their infants is not recommended since it is not known whether this drug is excreted in human milk. Stadol has been used safely for labor pain in mothers who subsequently nursed their infants.

Usage in Children: Safety and efficacy in children below age 18 years have not been established.

ADVERSE REACTIONS—The most frequent adverse reactions in 1250 patients treated with Stadol are: sedation (503, 40%), nausea (82, 6%), clammy/sweating (76, 6%).
Less frequent reactions are: headache (35, 3%), vertigo (33, 3%), floating feeling (33, 3%), dizziness (23, 2%), lethargy (19, 2%), confusion (15, 1%), lightheadedness (12, 1%).
Other adverse reactions which may occur (reported incidence of less than 1%) are:
CNS: nervousness, unusual dreams, agitation, euphoria, hallucinations
Autonomic: flushing and warmth, dry mouth, sensitivity to cold
Cardiovascular: palpitation, increase or decrease of blood pressure
Gastrointestinal: vomiting
Respiratory: slowing of respiration, shallow breathing
Dermatological: rash or hives
Eye: diplopia or blurred vision

OVERDOSAGE—Manifestations: Although there have been no experiences of overdosage with Stadol during clinical trials, this may occur due to accidental or intentional misuse as well as therapeutic use. Based on the pharmacology of Stadol, overdosage could produce some degree of respiratory depression and variable cardiovascular and central nervous system effects.

Treatment: The immediate treatment of suspected Stadol overdosage is intravenous naloxone. The respiratory and cardiac status of the patient should be evaluated constantly and appropriate supportive measures instituted, such as oxygen, intravenous fluids, vasopressors and assisted or controlled respiration.

HOW SUPPLIED—Stadol (butorphanol tartrate) Injection for I.M. or I.V. use, is available as follows:

NDC 0015-5644-20—2 mg per ml, 2-ml vial
NDC 0015-5645-20—1 mg per ml, 1-ml vial
NDC 0015-5646-20—2 mg per ml, 1-ml vial
NDC 0015-5646-23—2 mg per ml, 1-ml Disposable Syringe
NDC 0015-5648-20—2 mg per ml, 10-ml multi-dose vial

BRISTOL™

Bristol Laboratories
Division of Bristol-Myers Company
Syracuse, New York 13201

ADDRESS CHANGE NOTICE

International Anesthesia Research Society
3645 Warrensville Center Road
Cleveland, Ohio 44122

Please change my mail address for ANESTHESIA and ANALGESIA, effective

_____

From—(Current or former address)

_____

Street Address

_____

City, State, Zip Code

Important: Show your name and address exactly as your Journal is now addressed.

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To—(New Address)

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Street Address

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City, State, Zip Code

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Print Your Name



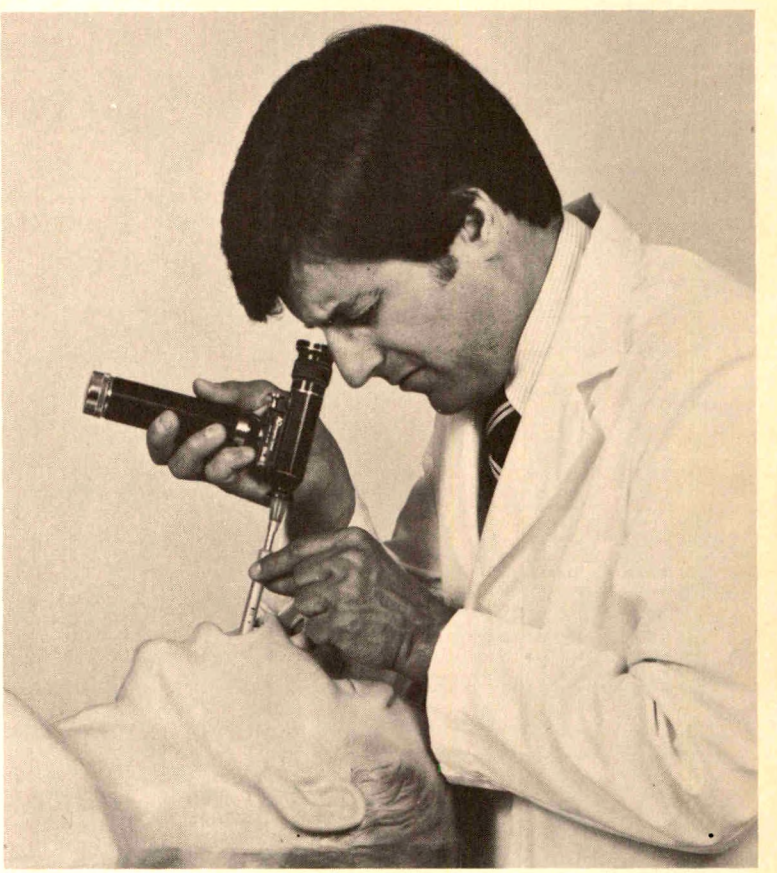
NEW HELP FOR MOST PROBLEM INTUBATIONS

The new American Optical Model SLS Stylet-Laryngoscope for oral intubation provides a clear view of oropharynx, larynx, and vocal cords as the endotracheal tube is gently but rapidly guided into position.

The small diameter (5.6 mm) AO stylet is malleable—it may be shaped for best entry regardless of patient position, injury or abnormality.

The easily used SLS allows intubation tube placement in cases where the standard blade laryngoscope is difficult to use due to obstructed vision, irregular intubation path, poor illumination or restricted oral opening.

SLS intubation procedure is similar to conventional laryngoscope technique.



Solve intubation problems-Request a demonstration.

American Optical Corporation, Fiber Optics, Southbridge, MA 01550

Name _____

Affiliation _____

Address _____

City _____ State _____ Zip _____

Phone _____ Ext. _____ Call between hours _____ & _____

☐ Arrange a demonstration of the AO SLS Stylet-Laryngoscope
☐ Send more information

AO®
American Optical

Fiber Optics, Southbridge, MA 01550
Phone (617) 765-9711, Extension 2445

Case record of an actual procedure*

HIP PINNING

ANESTHESIA RECORD

SUMMARY OF PRE OPERATIVE FINDINGS — SEX F — RACE — AGE 66 — WEIGHT 65 kg — HABITUS — TEETH OK

BP: 145/95 — T.P.R. 37.1°C/88/16 — HGB/HCT 11.8/38 — URINALYSIS Neg. — OTHER LAB DATA Electrolytes-WNL — FOOD INTAKE NPO — PRE-OP. VISIT yes

PHYSICAL STATUS: III — PRE OPER. DIAGNOSIS: Fracture R. hip

ANESTHESIOLOGIST 1. Dr. Kripke 2. — SURGEON 1. 2. 3. — REGION:

OPERATION PERFORMED: Hip Pinning, Bone Replacement

POST OPER. DIAGNOSIS:

PREMEDICATION:

TIME	DRUG AND ROUTE	EFFECT
6 45 AM	Innovar 1ml IM	Calm
	Atropine 0.3mg IM	& dry

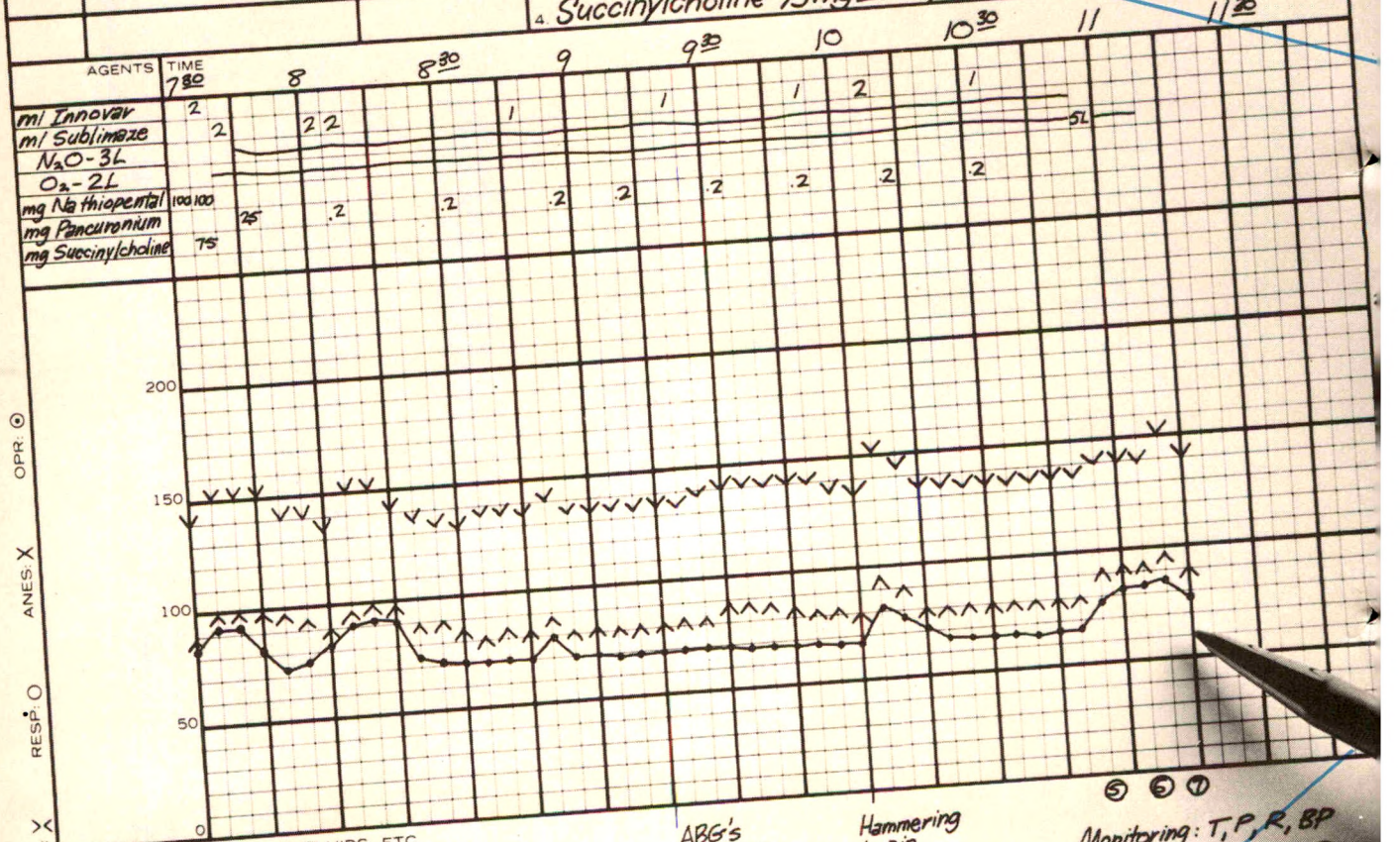
INDUCTION AGENTS

AGENT	DOSE OR METHOD
1. Na thiopental	200mg IV
2. Innovar	2ml IV
3. Sublimaze	2ml IV
4. Succinylcholine	75mg IV

MAINTENANCE AGENTS

AGENT	DOSE OR METHOD
1. N_2O-O_2	3L/2L
2. Sublimaze	10ml IV
3. Pancuronium	4.1 mg IV
4.	

TOTAL HRS: 11 20



REMARKS, MEDICATIONS, FLUIDS, ETC.

①②③④

Position – Supine
Blood – 2 units
D_5W – 500 ml
Ringers – 1500 in 500 runs

ABG's
O_2-175
CO_2-35
PH 7.45

Hammering in pin

⑤ ⑥ ⑦

Monitoring: T, P, R, BP
ECG, CVP
Art. Gases, Blocker

NOTES ON MANAGEMENT OF ANESTHESIA:

① Transfer to OR table after sleep dose pentothal
② Completion induction & intubation, no difficulty, teeth OK, ointment eyes, taped
③ Controlled ventilation, T25 cc/10 min./32 cm H_2O
④ Incision
⑤ Neostigmine 1.5 mg, Atropine 1.0 mg
⑥ Naloxone 95 µg IV
⑦ Extubate, to recovery room

R.R NOTES

Est. Blood loss ±850
BP 140/95 P 78, R 18
Condition excellent, patient respon
No N+V

TO WARD ☐ TO R R ☑ — POST-OP STATUS REFLEXES IN O.R. YES ☑ NO ☐ — AIRWAY TO ROOM YES ☐ NO ☑

© Janssen Pharmaceutica Inc. 1981 JPI-150

Charting the course of
balanced anesthesia

Innovar® INJECTION C II
(droperidol/fentanyl)

As premedication

- allays anxiety and apprehension
- reduces motor activity
- relieves pain and discomfort

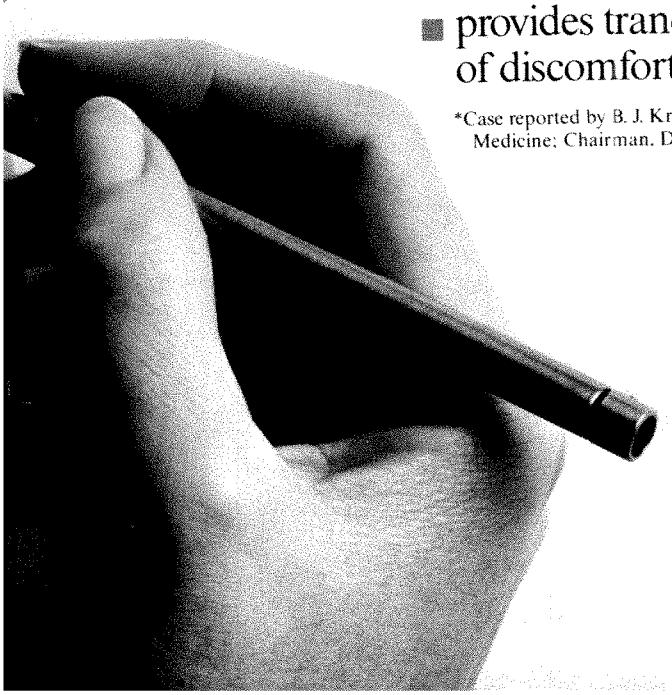
As an aid to induction

- facilitates intubation
- reduces amount of thiopental needed
- fosters a smooth, uneventful intraoperative course

In the postoperative period

- reduces incidence of nausea and vomiting
- reduces need for narcotic analgesics
- provides tranquilization and tolerance of discomfort

*Case reported by B. J. Kripke, M.D., Professor of Anesthesia, UCLA School of Medicine; Chairman, Dept. of Anesthesia, San Bernardino County Medical Center.



**Committed to research...
because so much
remains to be done.**

JANSSEN
PHARMACEUTICA

Janssen Pharmaceutica Inc., 501 George Street, New Brunswick, N.J. 08903

Please turn page for Brief Summary of Prescribing Information.

Innovar® Injection Ⓒ ℞

Protect from light. Store at room temperature.

Before prescribing, please consult complete prescribing information, of which the following is a brief summary.

FOR INTRAVENOUS OR INTRAMUSCULAR USE ONLY.

The two components of INNOVAR injection, fentanyl and droperidol, have different pharmacologic actions. Before administering INNOVAR injection, the user should familiarize himself with the special properties of each drug, particularly the widely differing durations of action.

DESCRIPTION: Each ml. contains (in a 1:50 ratio): Fentanyl, 0.05 mg. (as the citrate) *Warning:* May be habit forming; Droperidol, 2.5 mg.; Lactic acid for adjustment of pH to 3.5 ± 0.3.

CONTRAINDICATIONS: INNOVAR injection is contraindicated in patients with known intolerance to either component.

WARNINGS: AS WITH OTHER CNS DEPRESSANTS, PATIENTS WHO HAVE RECEIVED *INNOVAR* INJECTION SHOULD HAVE APPROPRIATE SURVEILLANCE. RESUSCITATIVE EQUIPMENT AND A NARCOTIC ANTAGONIST SHOULD BE READILY AVAILABLE TO MANAGE APNEA.

See also discussion of narcotic antagonists in PRECAUTIONS.

FLUIDS AND OTHER COUNTERMEASURES TO MANAGE HYPOTENSION SHOULD ALSO BE AVAILABLE.

The respiratory depressant effect of narcotics persists longer than the measured analgesic effect. When used with INNOVAR injection, the total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, be used in reduced doses initially, as low as ¼ to ⅓ those usually recommended.

INNOVAR injection may cause muscle rigidity, particularly involving the muscles of respiration. This effect is due to the fentanyl component and is related to the speed of injection. Its incidence can be reduced by the use of slow intravenous injection. Once the effect occurs, it is managed by the use of assisted or controlled respiration and, if necessary, by a neuromuscular blocking agent compatible with the patient's condition.

Drug Dependence: *Fentanyl, the narcotic analgesic component, can produce drug dependence of the morphine type and therefore has the potential for being abused.*

Severe and unpredictable potentiation by MAO inhibitors has been reported with narcotic analgesics. Since the safety of fentanyl in this regard has not been established, the use of INNOVAR injection or SUBLIMAZE (fentanyl) in patients who have received MAO inhibitors within 14 days is not recommended.

Head Injuries and Increased Intracranial Pressure: INNOVAR injection should be used with caution in patients who may be particulary susceptible to respiratory depression such as comatose patients who may have a head injury or brain tumor. In addition, INNOVAR injection may obscure the clinical course of patients with head injury.

Usage in Children: The safety of INNOVAR injection in children younger than two years of age has not been established.

Usage in Pregnancy: The safe use of INNOVAR injection has not been established with respect to possible adverse effects upon fetal development. Therefore, it should be used in women of childbearing potential only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. There are insufficient data regarding placental transfer and fetal effects; therefore, safety for the infant in obstetrics has not been established.

PRECAUTIONS: *The initial dose of INNOVAR injection should be appropriately reduced in elderly, debilitated and other poor-risk patients. The effect of the initial dose should be considered in determining incremental doses.* Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can alter respiration by blocking intercostal nerves, and can cause peripheral vasodilation and hypotension because of sympathetic blockade. Through other mechanisms, fentanyl and droperidol also depress respiration and blood pressure. Therefore, when INNOVAR injection is used to supplement these forms of anesthesia, the anesthetist must be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for this form of anesthesia.

If hypotension occurs, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should be considered when operative conditions permit. It should be noted that in spinal and peridural anesthesia, tilting the patient into a head down position may result in a higher level of anesthesia than is desirable, as well as impair venous return to heart. Care should be exercised in the moving and positioning of patients because of a possibility of orthostatic hypotension. If volume expansion with fluids plus these other countermeasures do not correct the hypotension, then the administration of pressor agents other than epinephrine should be considered. Epinephrine may paradoxically decrease the blood pressure in patients treated with INNOVAR injection due to the alpha-adrenergic blocking action of droperidol.

The droperidol component of INNOVAR injection may decrease pulmonary arterial pressure. This fact should be considered by those who conduct diagnostic or surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient.

Vital signs should be monitored routinely.

INNOVAR injection, and SUBLIMAZE (fentanyl), should be used with caution in patients with chronic obstructive pulmonary disease, patients with decreased respiratory reserve, and others with potentially compromised ventilation. In such patients narcotics may additionally decrease respiratory drive and increase airway resistance. During anesthesia this can be managed by assisted or controlled respiration. Postoperative respiratory depression caused by narcotic analgesics can be reversed by narcotic antagonists. Appropriate surveillance should be maintained because the duration of respiratory depression of doses of fentanyl (as SUBLIMAZE (fentanyl) or INNOVAR) employed during anesthesia may be longer than the duration of the narcotic antagonist action. Consult individual prescribing information (levallorphan, nalorphine and naloxone) before employing narcotic antagonists.

Should respiration be compromised by muscle rigidity, assisted or controlled respiration and possibly a neuromuscular blocking agent will be required. The occurrence of muscle rigidity is related to the speed of intravenous injection and the incidence can be reduced by slow intravenous injection.

Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, and general anesthetics) have additive or potentiating effects with INNOVAR injection. When patients have received such drugs, the dose of INNOVAR injection required will be less than usual. Likewise, following the administration of INNOVAR injection, the dose of other CNS depressant drugs should be reduced.

INNOVAR injection should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.

The fentanyl component may produce bradycardia, which may be treated with atropine; however, INNOVAR injection should be used with caution in patients with cardiac bradyarrhythmias.

When the EEG is used for postoperative monitoring, it may be found that the EEG pattern returns to normal slowly.

ADVERSE REACTIONS: The most common serious adverse reactions reported to occur with INNOVAR injection are respiratory depression, apnea, muscular rigidity, and hypotension; if these remain untreated, respiratory arrest, circulatory depression or cardiac arrest could occur.

Extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed following administration of INNOVAR injection. Restlessness, hyperactivity and anxiety which can be either the result of inadequate tranquilization or part of the symptom complex of akathisia may occur. When extrapyramidal symptoms occur, they can usually be controlled with anti-parkinson agents.

Elevated blood pressure, with and without preexisting hypertension, has been reported following administration of INNOVAR injection. This might be due to unexplained alterations of sympathetic activity following large doses; however, it is also frequently attributed to anesthetic or surgical stimulation during light anesthesia.

Other adverse reactions that have been reported are dizziness, chills and/or shivering, twitching, blurred vision, laryngospasm, bronchospasm, bradycardia, tachycardia, nausea and emesis, diaphoresis, emergence delirium, and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression).

Postoperative drowsiness is also frequently reported.

DOSAGE AND ADMINISTRATION: *Dosage should be individualized.* Some of the factors to be considered in determining dose are age, body weight, physical status, underlying pathological condition, use of other drugs, the type of anesthesia to be used, and the surgical procedure involved.

HOW SUPPLIED: INNOVAR® injection is supplied in 2 ml. and 5 ml. ampuls, in packages of 10.

Rev. 1/80

Sublimaze® (fentanyl) Injection Ⓒ ℞

Protect from light. Store at room temperature.

Before prescribing, please consult complete prescribing information, of which the following is a brief summary.

DESCRIPTION: Each ml. contains: Fentanyl, 0.05 mg. (as the citrate) *Warning:* May be habit forming; Sodium hydroxide for adjustment of pH to 4.0-7.5.

FOR INTRAVENOUS OR INTRAMUSCULAR USE ONLY.

CONTRAINDICATIONS: SUBLIMAZE (fentanyl) is contraindicated in patients with known intolerance to the drug.

WARNINGS: AS WITH OTHER CNS DEPRESSANTS, PATIENTS WHO HAVE RECEIVED *SUBLIMAZE* (FENTANYL) SHOULD HAVE APPROPRIATE SURVEILLANCE. RESUSCITATIVE EQUIPMENT AND A NARCOTIC ANTAGONIST SHOULD BE READILY AVAILABLE TO MANAGE APNEA.

See also discussion of narcotic antagonists in PRECAUTIONS.

If SUBLIMAZE (fentanyl) is administered with a tranquilizer such as INAPSINE (droperidol), the user should familiarize himself with the special properties of each drug, particularly the widely differing durations of action. In addition, when such a combination is used *fluids and other countermeasures to manage hypotension should be available.*

As with other potent narcotics, the respiratory depressant effect of SUBLIMAZE (fentanyl) persists longer than the measured analgesic effect. The total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, should be used in reduced doses initially, as low as ¼ to ⅓ those usually recommended. SUBLIMAZE (fentanyl) may cause muscle rigidity, particularly involving the muscles of respiration. The effect is related to the speed of injection and its incidence can be reduced by the use of slow intravenous injection. Once the effect occurs, it is managed by the use of assisted or controlled respiration and, if necessary, by a neuromuscular blocking agent compatible with the patient's condition.

Drug Dependence: SUBLIMAZE (fentanyl) can produce drug dependence of the morphine type and therefore has the potential for being abused.

Severe and unpredictable potentiation by MAO inhibitors has been reported with narcotic analgesics. Since the safety of fentanyl in this regard has not been established, the use of SUBLIMAZE (fentanyl) in patients who have received MAO inhibitors within 14 days is not recommended.

Head Injuries and Increased Intracranial Pressure: SUBLIMAZE (fentanyl) should be used with caution in patients who may be particularly susceptible to respiratory depression, such as comatose patients who may have a head injury or brain tumor. In addition, SUBLIMAZE (fentanyl) may obscure the clinical course of patients with head injury.

Usage in Children: The safety of SUBLIMAZE (fentanyl) in children younger than two years of age has not been established.

Usage in Pregnancy: The safe use of SUBLIMAZE (fentanyl) has not been established with respect to possible adverse effects upon fetal development. Therefore, it should be used in women of childbearing potential only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. There are insufficient data regarding placental transfer and fetal effects; therefore, safety for the infant in obstetrics has not been established.

PRECAUTIONS: *The initial dose of SUBLIMAZE (fentanyl) should be appropriately reduced in elderly, debilitated and other poor-risk patients. The effect of the initial dose should be considered in determining incremental doses.*

Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can alter respiration by blocking intercostal nerves. Through other mechanisms SUBLIMAZE (fentanyl) can also alter respiration. Therefore, when SUBLIMAZE (fentanyl) is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for these forms of anesthesia. When used with a tranquilizer such as INAPSINE (droperidol), blood pressure may be altered and hypotension can occur.

Vital signs should be monitored routinely.

SUBLIMAZE (fentanyl) should be used with caution in patients with chronic obstructive pulmonary disease, patients with decreased respiratory reserve, and others with potentially compromised respiration. In such patients, narcotics may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Respiratory depression caused by narcotic analgesics can be reversed by narcotic antagonists. Appropriate surveillance should be maintained because the duration of respiratory depression of doses of fentanyl during anesthesia may be longer than the duration of the narcotic antagonist action. Consult individual prescribing information (levallorphan, nalorphine and naloxone) before employing narcotic antagonists.

When a tranquilizer such as INAPSINE (droperidol) is used with SUBLIMAZE (fentanyl), pulmonary arterial pressure may be decreased. This fact should be considered by those who conduct diagnostic and surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient.

Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, and general anesthetics) will have additive or potentiating effects with SUBLIMAZE (fentanyl). When patients have received such drugs, the dose of SUBLIMAZE (fentanyl) required will be less than usual. Likewise, following the administration of SUBLIMAZE (fentanyl), the dose of other CNS depressant drugs should be reduced.

SUBLIMAZE (fentanyl) should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.

SUBLIMAZE (fentanyl) may produce bradycardia, which may be treated with atropine; however, SUBLIMAZE (fentanyl) should be used with caution in patients with cardiac bradyarrhythmias.

When SUBLIMAZE (fentanyl) is used with a tranquilizer such as INAPSINE (droperidol), hypotension can occur. If this occurs, the possibility of hypovolemia should also be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should be considered when operative conditions permit. Care should be exercised in moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do not correct hypotension, the administration of pressor agents other than epinephrine should be considered. Because of the alpha-adrenergic blocking action of INAPSINE (droperidol), epinephrine may paradoxically decrease the blood pressure in patients treated with INAPSINE (droperidol). When INAPSINE (droperidol) is used with SUBLIMAZE (fentanyl) and the EEG is used for postoperative monitoring, it may be found that the EEG pattern returns to normal slowly.

ADVERSE REACTIONS: As with other narcotic analgesics, the most common serious adverse reactions reported to occur with SUBLIMAZE (fentanyl) are respiratory depression, apnea, muscular rigidity, and bradycardia; if these remain untreated, respiratory arrest, circulatory depression or cardiac arrest could occur. Other adverse reactions that have been reported are hypotension, dizziness, blurred vision, nausea, emesis, laryngospasm, and diaphoresis.

When a tranquilizer such as INAPSINE (droperidol) is used with SUBLIMAZE (fentanyl), the following adverse reactions can occur: chills and/or shivering, restlessness, and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression); extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed up to 24 hours postoperatively. When they occur, extrapyramidal symptoms can usually be controlled with anti-parkinson agents. Postoperative drowsiness is also frequently reported following the use of INAPSINE (droperidol).

Elevated blood pressure, with and without preexisting hypertension, has been reported following administration of SUBLIMAZE (fentanyl) combined with INAPSINE (droperidol). This might be due to unexplained alterations in sympathetic activity following large doses; however, it is also frequently attributed to anesthetic and surgical stimulation during light anesthesia.

DOSAGE AND ADMINISTRATION: *Dosage should be individualized.* Some of the factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and the surgical procedure involved.

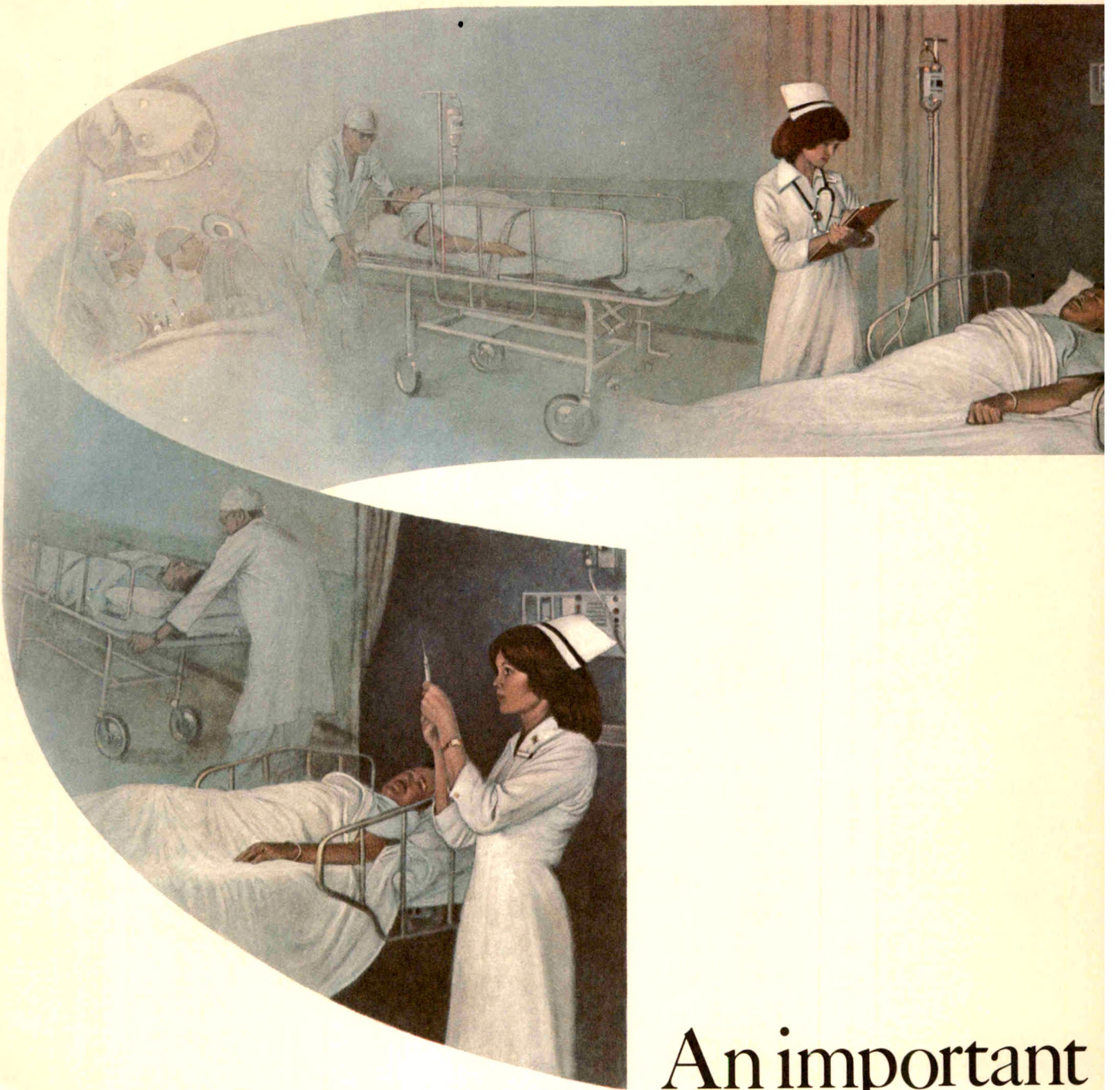
HOW SUPPLIED: 2 ml. and 5 ml. ampuls—packages of 10.

Rev. 1/80

Committed to research ... because so much remains to be done.

JANSSEN PHARMACEUTICA

Janssen Pharmaceutica Inc, 501 George St., New Brunswick, N.J. 08903



An important new preanesthetic medication

New ATIVAN® (LORAZEPAM) IV INJECTION IM or IV

See important information on last page.

Ativan® (lorazepam) Injection satisfies important criteria for successful premedication

As confirmed in multicenter studies involving 2631 patients[1]

Leaves the patient sedated, yet cooperative

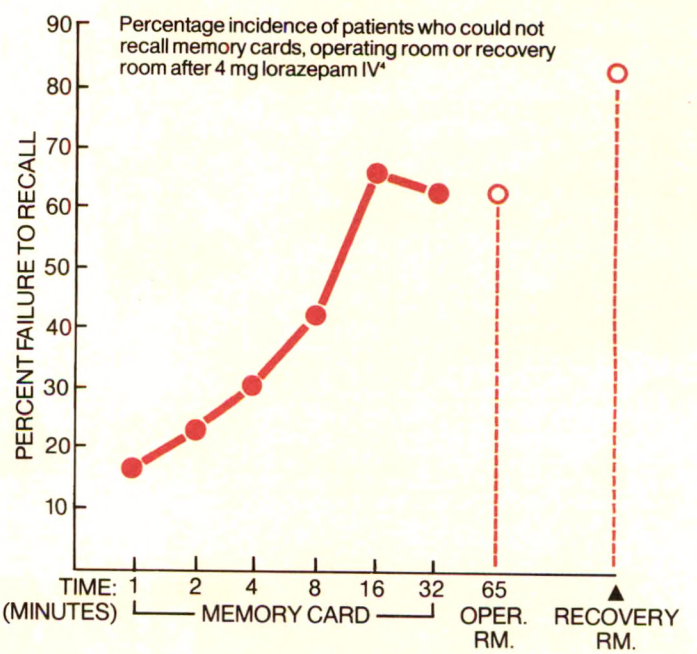
In contrast to older preanesthetic medication, the majority of patients premedicated with Ativan Injection, though clinically sedated, are able to respond to simple instructions, whether they give the appearance of being awake or asleep.[2]

Allays preoperative apprehension

Ativan Injection significantly reduces the level of preoperative anxiety.[3,4] It is especially useful in patients who suffer anticipatory anxiety and those who would prefer not to remember their surgical experience.

Blocks or diminishes recall for 6-8 hours after a single injection

The majority of patients premedicated with Ativan Injection have difficulty remembering perisurgical events. This lack of recall is relative, rather than absolute, as determined under conditions of careful patient questioning and testing, using "memory cards" designed to enhance recall.[4,5]



Rated "highly acceptable" by most patients

The effect produced by Ativan Injection is rated as "highly acceptable" by a majority of patients. When questioned after their operation, virtually all indicated they would wish to receive Ativan Injection again for any future surgery.[1]

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Effective IM and IV

"Lorazepam may also fill the pressing need for a benzodiazepine with prompt and reliable clinical action when given by *intramuscular injection*."[6]* And, in contrast to diazepam, the metabolism of Ativan is simple and does not involve long-acting metabolites.

Vital signs—essentially normal

In most patients, Ativan Injection has only minimal effects on blood pressure, pulse and respiratory rate. Hypertension (0.1%) and hypotension (0.1%) have been reported very rarely.

Little if any IV irritation

In contrast to the thrombophlebitis frequently seen with older premedication, Ativan Injection when properly diluted has only minimal irritative or injurious effects on the veins.[7] A painful response to IV injection was noted in 13 of 771 patients (1.6%), of whom 4 (0.5%) still complained of pain 24 hrs later.[1]

Can be used with most anesthetic agents

Ativan Injection can be used with atropine sulfate, narcotic analgesics, other parenterally used analgesics, commonly used anesthetics and muscle relaxants. Concomitant use with scopolamine is not advisable, since it may lead to increased sedation, hallucinations and irrational behavior.

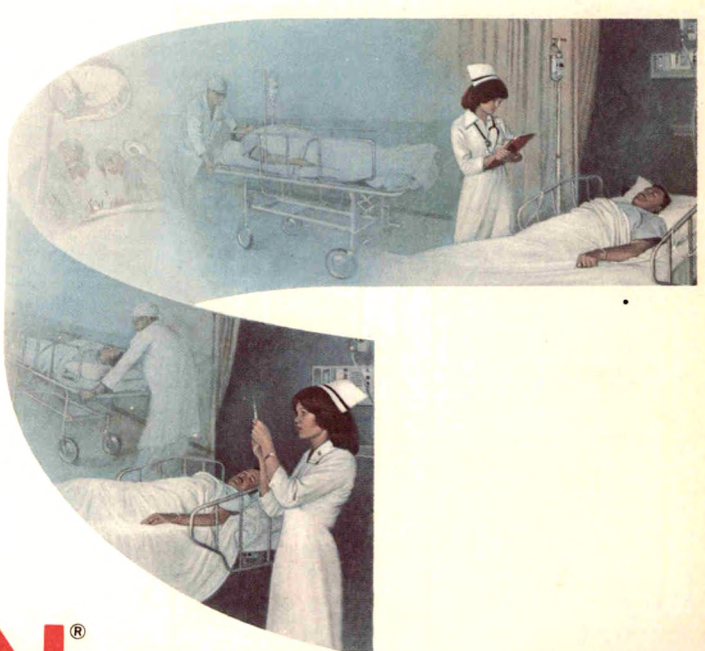
*emphasis added

Ativan Injection is available in TUBEX® sterile cartridge-needle units for single use and in multiple-dose vials.

References:

1. Data on file, Wyeth Laboratories.
2. Simpson PJ, Eltringham RJ: to be published.
3. Conner JT, Parson N, Katz RL, et al: Clin Pharmacol Ther *19*:24-29, 1976.
4. Conner JT, Katz RL, Bellville JW, et al: J Clin Pharmacol *18*:285-292, 1978.
5. Heisterkamp DV, Cohen PJ: Br J Anaesth *47*:79-81, 1975.
6. Greenblatt DJ, Shader RI: N Engl J Med *299*:1342-1344, 1978.
7. Graham CW, Pagano RR, Conner JT: Anaesthesia *33*:188-191, 1978.

To arrange a showing of the film "Preoperative Medication and the Role of ATIVAN® (lorazepam) Injection," call or write Wyeth or your Wyeth representative.



Wyeth Laboratories
Philadelphia, PA 19101
TM

New ATIVAN® (LORAZEPAM) IV INJECTION IM or IV

See important information on last page.

An important new preanesthetic medication

ATIVAN® (LORAZEPAM) IV INJECTION IM or IV

DESCRIPTION: Ativan® (lorazepam) Injection, a benzodiazepine with antianxiety and sedative effects, is intended for IM or IV use. It has the chemical formula 7-chloro-5-(*o*-chlorophenyl)-1,3-dihydro-3-hydroxy-2*H*-1,4-benzodiazepin-2-one.

Lorazepam is a nearly white powder almost insoluble in water. Each ml of sterile injection contains either 2.0 or 4.0 mg lorazepam, 0.18 ml polyethylene glycol 400 in propylene glycol with 2.0% benzyl alcohol as preservative.

CLINICAL PHARMACOLOGY: IV or IM administration of recommended dose of 2-4 mg lorazepam injection to adult patients is followed by dose related effects of sedation (sleepiness or drowsiness), relief of preoperative anxiety and lack of recall of events related to day of surgery in most patients. The clinical sedation (sleepiness or drowsiness) thus noted is such that most patients are able to respond to simple instructions whether they give appearance of being awake or asleep. Lack of recall is relative rather than absolute, as determined under conditions of careful patient questioning and testing, using props designed to enhance recall. Most patients under these reinforced conditions had difficulty recalling perioperative events, or recognizing props from before surgery. Lack of recall and recognition was optimum within 2 hours after IM and 15-20 minutes after IV injection.

Intended effects of recommended adult dose of lorazepam injection usually last 6-8 hours. In rare instances and where patients received greater than recommended dose, excessive sleepiness and prolonged lack of recall were noted. As with other benzodiazepines, unsteadiness, enhanced sensitivity to CNS depressant effects of ethyl alcohol and other drugs were noted in isolated and rare cases for greater than 24 hours.

Studies in healthy adult volunteers reveal that IV lorazepam in doses up to 3.5 mg/70 kg does not alter sensitivity to respiratory stimulating effect of carbon dioxide and does not enhance respiratory depressant effects of doses of meperidine up to 100 mg/70 kg (also determined by carbon dioxide challenge) as long as patients remain sufficiently awake to undergo testing. Upper airway obstruction was observed in rare instances where the patient received greater than recommended dose, and was excessively sleepy and difficult to arouse. (See WARNINGS and ADVERSE REACTIONS.)

Clinically employed doses of lorazepam injectable do not greatly affect the circulatory system in the supine position or employing a 70 degree tilt test. Doses of 8-10 mg of IV lorazepam (2 to 2.5 times maximum recommended dosage) will produce loss of lid reflexes within 15 minutes.

Studies in six (6) healthy young adults who received lorazepam injection and no other drugs revealed that visual tracking (the ability to keep a moving line centered) was impaired for a mean of eight (8) hours following 4 mg IM lorazepam and four (4) hours following 2 mg IM with considerable subject variation. Similar findings were noted with pentobarbital 150 and 75 mg. Although this study showed both lorazepam and pentobarbital interfered with eye-hand coordination, data are insufficient to predict when it would be safe to operate a motor vehicle or engage in hazardous occupation or sport.

INDICATIONS AND USAGE: In adults—for preanesthetic medication, producing sedation (sleepiness or drowsiness), relief of anxiety, and decreased ability to recall events related to day of surgery. Most useful in patients anxious about surgical procedure who prefer diminished recall of events of day of surgery.

CONTRAINDICATIONS: Known sensitivity to benzodiazepines or vehicle (polyethylene glycol, propylene glycol, and benzyl alcohol) or acute narrow angle glaucoma. Intra-arterial injection is contraindicated because, as with other injectable benzodiazepines, inadvertent intra-arterial injection may produce arteriospasm resulting in gangrene which may require amputation. (See Warnings)

WARNINGS: PRIOR TO IV USE, LORAZEPAM SHOULD BE DILUTED WITH EQUAL AMOUNT OF COMPATIBLE DILUENT (SEE DOSAGE AND ADMINISTRATION). IV INJECTION SHOULD BE MADE SLOWLY AND WITH REPEATED ASPIRATION. CAREFULLY DETERMINE THAT INJECTION WILL NOT BE INTRA-ARTERIAL AND PERIVASCULAR EXTRAVASATION WILL NOT OCCUR. PARTIAL AIRWAY OBSTRUCTION MAY OCCUR IN HEAVILY SEDATED PATIENTS. IV LORAZEPAM, GIVEN ALONE IN GREATER THAN RECOMMENDED DOSE, OR AT RECOMMENDED DOSE AND ACCOMPANIED BY OTHER DRUGS USED DURING ANESTHESIA, MAY PRODUCE HEAVY SEDATION; THEREFORE, EQUIPMENT TO MAINTAIN PATENT AIRWAY AND SUPPORT RESPIRATION AND VENTILATION SHOULD BE AVAILABLE.

No evidence now supports lorazepam injection in coma, shock or acute alcohol intoxication. Since the liver is the most likely site of conjugation and since excretion of conjugated lorazepam (glucuronide), is renal, lorazepam is not recommended in hepatic and/or renal *failure*. This does not preclude its use in patients with mild to moderate hepatic or renal disease. When injectable lorazepam is used in mild to moderate hepatic or renal disease, consider lowest effective dose since drug effect may be prolonged. Experience with other benzodiazepines and limited experience with parenteral lorazepam demonstrated that tolerance to concomitant alcohol and other CNS depressants is diminished. As with similar CNS-acting drugs, patients receiving injectable lorazepam should not operate machinery or motor vehicles or engage in hazardous occupations for 24 to 48 hours. Impairment of performance may persist for greater intervals because of extremes of age, other concomitant drugs, stress of surgery or general condition of patient. Clinical trials showed patients over 50 may have more profound and prolonged sedation with IV use. Ordinarily an initial dose of 2 mg may be adequate, unless greater degree of lack of recall is desired. As with all CNS depressants, exercise care in patients given injectable lorazepam since premature ambulation may result in injury from falling. There is no added beneficial effect from adding scopolamine to injectable lorazepam; their combined effect may result in increased incidence of sedation, hallucination and irrational behavior.

Pregnancy: LORAZEPAM GIVEN TO PREGNANT WOMEN MAY CAUSE FETAL DAMAGE. Increased risk of congenital malformations with use of minor tranquilizers (chlordiazepoxide, diazepam, meprobamate) during first trimester of pregnancy was suggested in several studies. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide. Lorazepam injection should not be used during pregnancy because of insufficient data on obstetrical safety, including its use in cesarean section. Reproductive studies performed in mice, rats, and two strains of rabbits showed occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in concurrent control group, they have been reported to occur randomly in historical controls. At doses of 40 mg/kg p.o. or 4 mg/kg IV and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses.

Endoscopic Procedures: There are insufficient data to support lorazepam injection for outpatient endoscopic procedures. Inpatient endoscopic procedures require adequate recovery room observations. Pharyngeal reflexes are not impaired when lorazepam injection is used for per-oral endoscopic procedures, therefore adequate topical or regional anesthesia is recommended to minimize reflex activity associated with such procedures.

PRECAUTIONS: General: Bear in mind additive CNS effects of other drugs, e.g. phenothiazines, narcotic analgesics, barbiturates, antidepressants, scopolamine and MAO inhibitors when these drugs are used concomitantly with or during period of recovery from lorazepam injection. (See CLINICAL PHARMACOLOGY and WARNINGS.) Use extreme care in giving lorazepam injection to elderly or very ill patients, or those with limited pulmonary reserve, because of possible underventilation and/or hypoxic cardiac arrest. Resuscitative equipment for ventilatory support should be readily available. (See WARNINGS and DOSAGE and ADMINISTRATION.) When lorazepam is used IV as premedicant prior to regional or local anesthesia, excessive sleepiness or drowsiness may possibly interfere with patient cooperation to determine anesthesia levels. This is most likely when more than 0.05 mg/kg is given and narcotic analgesics are used concomitantly with the recommended dose. (See ADVERSE REACTIONS.)

Information for Patients: As appropriate, inform patients of pharmacological effects, e.g. sedation, relief of anxiety and lack of recall, and duration of these effects (about 8 hours), so they may adequately perceive risks as well as benefits from its use. Caution patients who receive lorazepam injection as premedicant that driving automobiles or operating hazardous machinery, or engaging in hazardous sports should be delayed for 24 to 48 hours after injection. Sedatives, tranquilizers, and narcotic analgesics given with injectable lorazepam may produce more prolonged and profound effect, taking the form of excessive sleepiness or drowsiness, and rarely interfering with recall and recognition of events of day of surgery and the day after. Getting out of bed unassisted may result in falling and injury if undertaken within 8 hours of receiving lorazepam injection. Alcoholic beverages should not be used for at least 24 to 48 hours after lorazepam injection due to additive effects on CNS depression seen with benzodiazepines in general. Elderly patients should be told lorazepam injection may make them very sleepy for longer than 6 to 8 hours after surgery.

Laboratory Tests: In clinical trials no laboratory test abnormalities were identified with single or multiple doses of lorazepam injection. Tests included: CBC, urinalysis, SGOT, SGPT, bilirubin, alkaline phosphatase, LDH, cholesterol, uric acid, BUN, glucose, calcium, phosphorus and total proteins.

Drug Interactions: Lorazepam injection, like other injectable benzodiazepines, produces CNS depression when given with ethyl alcohol, phenothiazines, barbiturates, MAO inhibitors and other antidepressants. When scopolamine is used concomitantly with injectable lorazepam increased incidence of sedation, hallucinations and irrational behavior was observed.

Drug/Laboratory Test Interactions: No laboratory test abnormalities were identified when lorazepam was given alone or concomitantly with another drug, e.g. narcotic analgesics, inhalation anesthetics, scopolamine, atropine, and various tranquilizing agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No evidence of carcinogenic potential emerged in rats and mice during an 18-month study with oral lorazepam. No studies regarding mutagenesis have been performed. Pre-implantation study in rats, performed with oral lorazepam at a 20 mg/kg dose, showed no impairment of fertility.

Pregnancy: Pregnancy Category D. See WARNINGS section.

Labor and Delivery: There are insufficient data for lorazepam injection in labor and delivery, including cesarean section; therefore, this use is not recommended.

Nursing Mothers: Do not give injectable lorazepam to nursing mothers, because like other benzodiazepines, lorazepam may possibly be excreted in human milk and sedate the infant.

Pediatric Use: There are insufficient data to support efficacy or make dosage recommendations for injectable lorazepam in patients under 18 years; therefore, such use is not recommended.

ADVERSE REACTIONS: CNS: Most frequent adverse effects with injectable lorazepam are extensions of drug's CNS depressant effects. Incidence varied from one study to another, depending on dosage, route, use of other CNS depressants, and investigator's opinion concerning degree and duration of desired sedation. Excessive sleepiness and drowsiness were main side effects. This interfered with patient cooperation in about 6% (25/446) of patients undergoing regional anesthesia in that they were unable to assess levels of anesthesia in regional blocks or with caudal anesthesia. Patients over 50 years had higher incidence of excessive sleepiness or drowsiness compared with those under 50 (21/106 vs 24/245) when lorazepam was given IV (see DOSAGE and ADMINISTRATION). On rare occasion (3/1580) patient was unable to give personal identification on arrival in operating room, and one patient fell when attempting premature ambulation in postoperative period. Symptoms such as restlessness, confusion, depression, crying, sobbing, and delirium occurred in about 1.3% (20/1580). One patient injured himself postoperatively by picking at his incision. Hallucinations were present in about 1% (14/1580) of patients, and were visual and self-limiting. An occasional patient complained of dizziness, diplopia and/or blurred vision. Depressed hearing was infrequently reported during peak effect period. An occasional patient had prolonged recovery room stay, because of excessive sleepiness or some form of inappropriate behavior (latter seen most commonly when scopolamine given concomitantly as premedicant). Limited information from patients discharged day after receiving injectable lorazepam showed one patient complained of some unsteadiness of gait and reduced ability to perform complex mental functions. Enhanced sensitivity to alcoholic beverages was reported more than 24 hours after injectable lorazepam, similar to experience with other benzodiazepines.

Local Effects: IM lorazepam resulted in pain at injection site, a sensation of burning, or observed redness in the same area in a very variable incidence from one study to another. Overall incidence of pain and burning was about 17% (146/859) in immediate postinjection period, and about 1.4% (12/859) at 24-hour observation time. Reactions at injection site (redness) occurred in about 2% (17/859) in immediate postinjection period, and were present 24 hours later in about 0.8% (7/859). IV lorazepam resulted in pain in 13/771 patients or about 1.6% immediately post-injection and 24 hours later 4/771 patients or about 0.5% still complained of pain. Redness did not occur immediately post IV but was noted in 19/771 patients at 24-hour period (incidence is similar to that observed with IV infusion before lorazepam was given).

Cardiovascular System: Hypertension (0.1%) and hypotension (0.1%) were occasionally observed after patients received injectable lorazepam.

Respiratory System: Five patients (5/446) who underwent regional anesthesia were observed to have partial airway obstruction. This was believed due to excessive sleepiness at time of procedure, and resulted in temporary underventilation. Immediate attention to the airway, employing usual countermeasures, will usually suffice to manage this (see also CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS).

Other Adverse Experiences: Skin rash, nausea and vomiting were occasionally noted in patients who received injectable lorazepam with other drugs during anesthesia and surgery.

DRUG ABUSE AND DEPENDENCE: As with other benzodiazepines, lorazepam injection has a low potential for abuse and may lead to limited dependence. Although there are no such clinical data for injectable lorazepam, repeated doses over prolonged period of time may result in limited physical and psychological dependence.

OVERDOSAGE: Overdosage of benzodiazepines is usually manifested by varying degrees of CNS depression ranging from drowsiness to coma. In mild cases symptoms include drowsiness, mental confusion and lethargy; in more serious cases ataxia, hypotonia, hypotension, hypnosis, stages one to three coma, and very rarely death. Treatment of overdosage is mainly supportive until drug is eliminated. Carefully monitor vital signs and fluid balance. Maintain adequate airway and assist respiration as needed. With normally functioning kidneys, forced diuresis with intravenous fluids and electrolytes may accelerate elimination of benzodiazepines. In addition, osmotic diuretics such as mannitol may be effective as adjunctive measures. In more critical situations, renal dialysis and exchange blood transfusions may be indicated. Published reports indicate that IV infusion of 0.5 to 4 mg physostigmine at rate of 1 mg/minute may reverse symptoms and signs suggestive of central anticholinergic overdose (confusion, memory disturbance, visual disturbances, hallucinations, delirium); however, hazards associated with physostigmine (i.e., induction of seizures) should be weighed against possible clinical benefit.

DOSAGE AND ADMINISTRATION: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Do not use if solution is discolored or contains a precipitate.

Intramuscular Injection: For designated indications as premedicant, usual IM dose of lorazepam is 0.05 mg/kg up to maximum of 4 mg. As with all premedicants, individualize dose. (See also CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.) Doses of other CNS depressants should ordinarily be reduced. (See PRECAUTIONS.) *For optimum effect, measured as lack of recall, administer lorazepam IM at least 2 hours before anticipated operative procedure.* Administer narcotic analgesics at usual preoperative time. There are insufficient efficacy data to make dosage recommendations for IM lorazepam in patients under 18 years; therefore, such use is not recommended.

Intravenous Injection: For the primary purpose of sedation and relief of anxiety, usual recommended initial IV dose of lorazepam is 2 mg total, or 0.02 mg/lb (0.044 mg/kg), whichever is smaller. This dose will suffice for sedating most adults, and should not ordinarily be exceeded in patients over 50 years. In patients in whom greater likelihood of lack of recall for perioperative events would be beneficial, larger doses—as high as 0.05 mg/kg up to total of 4 mg—may be given. (See CLINICAL PHARMACOLOGY, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS.) Doses of other injectable CNS depressants should ordinarily be reduced. (See PRECAUTIONS.) *For optimum effect, measured as lack of recall, IV lorazepam should be administered 15-20 minutes before anticipated operative procedure.* EQUIPMENT NECESSARY TO MAINTAIN A PATENT AIRWAY SHOULD BE IMMEDIATELY AVAILABLE PRIOR TO IV USE OF LORAZEPAM (see WARNINGS). There are insufficient efficacy data to make dosage recommendations for IV lorazepam in patients under 18 years; therefore, such use is not recommended.

Administration: When given IM, lorazepam injection, undiluted, should be injected deep in muscle mass. Injectable lorazepam can be used with atropine sulfate, narcotic analgesics, other parenterally used analgesics, commonly used anesthetics, and muscle relaxants. Immediately prior to IV use, lorazepam injection must be diluted with an equal volume of compatible solution. When properly diluted the drug may be injected directly into a vein or into the tubing of an existing IV infusion. Rate of injection should not exceed 2.0 mg per minute. Lorazepam injection is compatible for dilution purposes with: Sterile Water for Injection, USP, Sodium Chloride Injection, USP, 5% Dextrose Injection, USP.

HOW SUPPLIED: Ativan® (lorazepam) injection, Wyeth, is available in multiple-dose vials and in TUBEX® Sterile Cartridge-Needle Units.

2 mg/ml, NDC 0008-0581; 10 ml vial and 1 ml fill in 2 ml TUBEX.
4 mg/ml, NDC 0008-0570; 10 ml vial and 1 ml fill in 2 ml TUBEX.

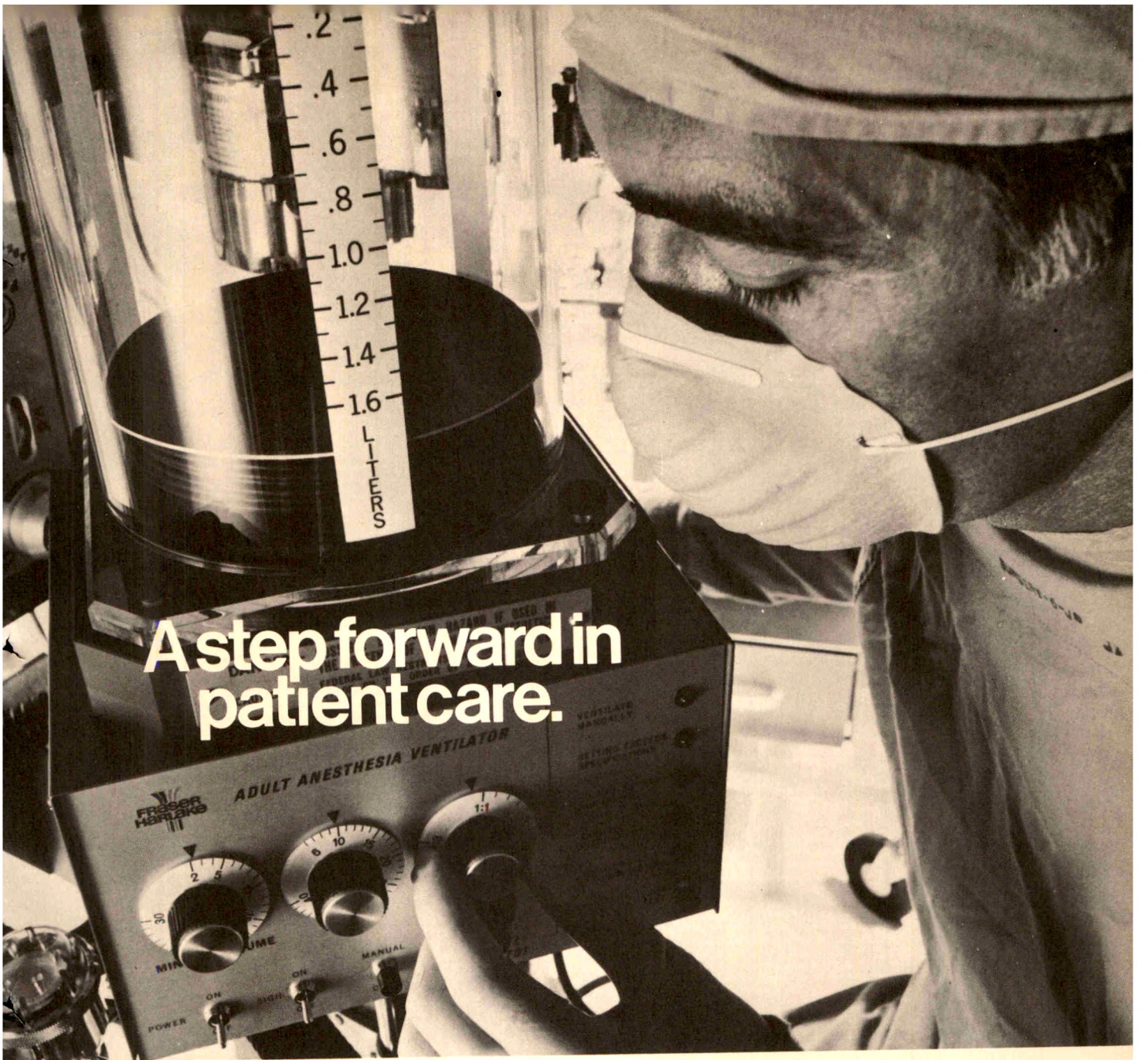
For IM or IV injection.

Protect from light. Keep in refrigerator.

Directions for Dilution for IV Use: To dilute, adhere to following procedure: For TUBEX—(1) Extrude entire amount of air in half-filled TUBEX. (2) Slowly aspirate desired volume of diluent. (3) Pull back slightly on plunger to provide additional mixing space. (4) Immediately mix contents thoroughly by gently inverting TUBEX repeatedly until homogenous solution results. Do not shake vigorously, as this will result in air entrapment. For Vial—Aspirate desired amount of lorazepam injection into syringe. Then proceed as described under TUBEX.

Wyeth Laboratories
Philadelphia, PA 19101

CI3117-1 7/31/80



A step forward in patient care.

Accuracy, simplicity and safety. We've made these the three primary characteristics of our 700 and 701 Anesthesia Ventilators. The special features that make them unique also make these Fraser Harlake Ventilators the most functional models available today.

Non-interacting physiological controls. Only three dials, all with linear calibrations, for greater accuracy as well as easier operation. The 701 Ventilator can be set to deliver exact Minute Volume, Rate, and I:E Ratio for proper patient ventilation.

Built-in safety features. The 701 Ventilator features the most complete warning system available. Alarms—both audible and visible—are triggered if setting exceeds specifications; gas supply pressure is low; actual I:E is less than dial setting; patient is disconnected, or power is disconnected. These alarms monitor both the patient and the machine, and continue until the problem is corrected.

Pediatric bellows assembly. Designed for the pediatric patient in surgery with Tidal Volume less than 300 milliliters. Both the Model 700 and the Model 701 Ventilators can be converted for pediatric use by replacing the adult bellows assembly with the pediatric bellows assembly.

And more. Solid-state circuity insures a high degree of accuracy and patient safety. Separate mounting for control module and bellows assembly provides flexibility. Human engineered for convenient use.

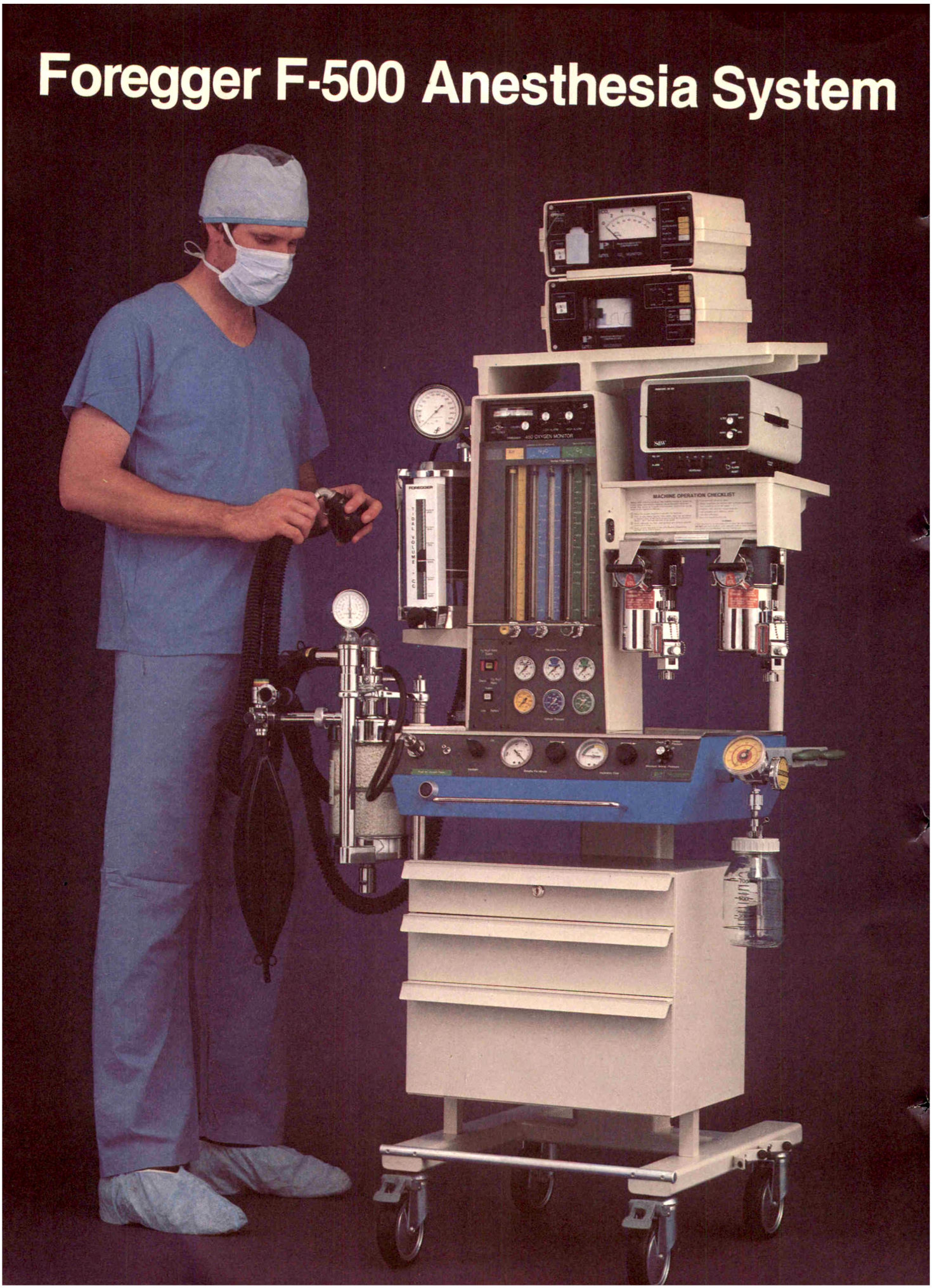
For more information on the Model 700 and Model 701 Anesthesia Ventilators, contact Fraser Harlake.

An important innovation in patient care.



FRASER HARLAKE

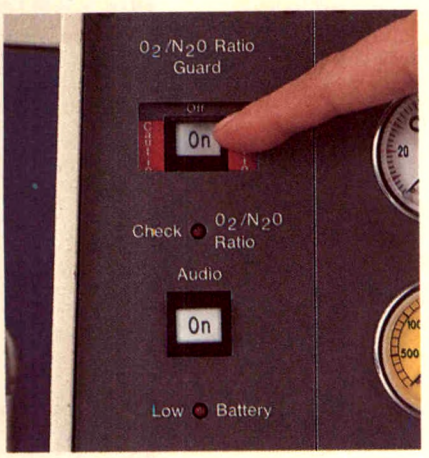
Foregger F-500 Anesthesia System



Designed With . . .
The Anesthesiologist In Mind

Safe . . . Easy To Use And Understand . . . Compact . . . Sturdy . . . Accessible Controls . . . Ample Monitoring Space

These are the features anesthesiologist told us they wanted incorporated in a new machine - requirements we've met with the all-new Foregger F-500.



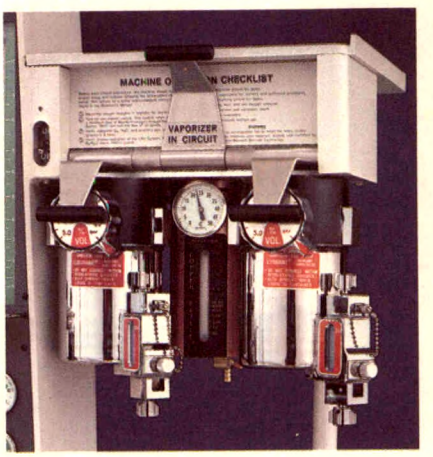
O_2/N_2O Ratio Protection And Alarm System

In addition to our conventional protection, the new O_2/N_2O Protection and Alarm System guards against the possibility of inadvertent hypoxic mixtures. Three systems of O_2/N_2O ratio protection are offered:

System 1 allows the operator to set any desired O_2 concentration from a nominal 26% O_2 to 100% O_2. Oxygen flow is automatically augmented to maintain a minimum 26% O_2 ratio if the operator attempts to reduce the ratio below 26%. When O_2 is augmented, an audible and visible alarm is activated.

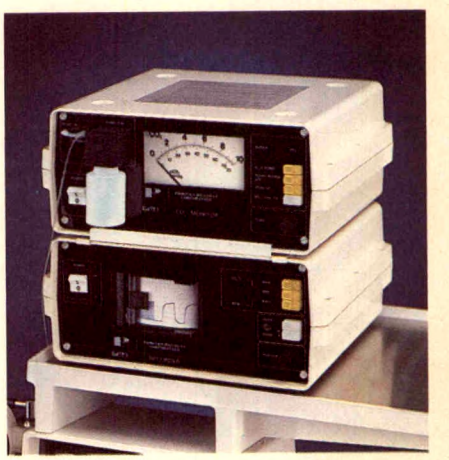
System 2 allows the operator to set any desired O_2/N_2O ratio. If the mixture selected is below 26% O_2 concentration, the operator is alerted by an audible and visible alarm.

System 3 combines the features of system 1 and 2. A push-button allows the operator to switch from one system to the other.



Tri-Lock™ Vaporizer Protection

Gas flow through the vaporizer is controlled by the Tri-Lock Vaporizer System to help prevent the simultaneous delivery of more than one agent. This is accomplished by isolating all vaporizers from common circuitry and by allowing only one vaporizer to be engaged at a time.



Puritan-Bennett/Datex End-Tidal CO_2 Monitor

Ventilatory nomograms often have a built-in safety margin that can lead to hyperventilation and concomitantly, hypocapnia with alkalemia. On the F-500, an optional CO_2 Monitor and Strip-Chart Recorder continuously monitors respiratory CO_2 levels of the patient to provide a rapid accurate indicator of ventilatory/respiratory efficiency regardless of controlled or spontaneous ventilation.

For more information about the Foregger F-500, contact your local Dealer or Representative or write:

Puritan-Bennett Corporation
Foregger Medical Division
835 Wheeler Way
Langhorne, PA 19047

PURITAN-BENNETT CORPORATION | FOREGGER MEDICAL DIVISION

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See below for important product information concerning warnings, adverse reactions, patient selection and prescribing and precautionary recommendations.

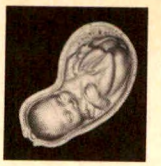
More protection for the newborn

Marcaine® hydrochloride

brand of

bupivacaine hydrochloride

with or without epinephrine 1:200,000



Indications: Peripheral nerve block, infiltration, sympathetic block, caudal, or epidural block.

Contraindication: Marcaine is contraindicated in patients with known hypersensitivity to it.

Warnings: RESUSCITATIVE EQUIPMENT AND DRUGS SHOULD BE READILY AVAILABLE WHEN ANY LOCAL ANESTHETIC IS USED.

Usage in Pregnancy. Reproduction studies have been performed in rats and rabbits and there is no evidence of harm to the animal fetus. The relevance to the human is not known. Safe use in pregnant women other than those in labor has not been established.

Until further clinical experience is gained, paracervical block with Marcaine is not recommended. Fetal bradycardia frequently follows paracervical block with some amide-type local anesthetics and may be associated with fetal acidosis. Added risk appears to be present in prematurity, toxemia of pregnancy, and fetal distress.

The obstetrician is warned that severe persistent hypertension may occur after administration of certain oxytocic drugs, if vasopressors have already been used during labor (e.g., in the local anesthetic solution or to correct hypotension).

Solutions containing a vasoconstrictor, particularly epinephrine or norepinephrine, should be used with extreme caution in patients receiving monoamine oxidase (MAO) inhibitors or antidepressants of the triptyline or imipramine types, because severe, prolonged hypertension may result.

Local anesthetics which contain preservatives, i.e., those supplied in multiple dose vials, should not be used for caudal or epidural anesthesia.

Until further experience is gained in children younger than 12 years, administration of Marcaine in this age group is not recommended.

Precautions: The safety and effectiveness of local anesthetics depend upon proper dosage, correct technique, adequate precautions, and readiness for emergencies.

The lowest dosage that gives effective anesthesia should be used in order to avoid high plasma levels and serious systemic side effects. Injection of repeated doses of Marcaine may cause significant increase in blood levels with each additional dose, due to accumulation of the drug or its metabolites or due to slow metabolic degradation. Tolerance varies with the status of the patient. Debilitated, elderly patients and acutely ill patients should be given reduced doses commensurate with age and physical condition.

Solutions containing a vasoconstrictor should be used cautiously in areas with limited blood supply, in the presence of diseases that may adversely affect the patient's cardiovascular system, or in patients with peripheral vascular disease.

Marcaine should be used cautiously in persons with known drug allergies or sensitivities, particularly to the amide-type local anesthetics.

Serious dose-related cardiac arrhythmias may occur if preparations containing a vasoconstrictor such as epinephrine are employed in patients during or following the administration of chloroform, halothane, cyclopropane, trichloroethylene, or other related agents. In deciding whether to use these products concurrently in the same patient, the combined action of both agents upon the myocardium, the concentration and volume of vasoconstrictor used, and the time since injection, when applicable, should be taken into account.

Caution is advised in administration of repeat doses of Marcaine to patients with severe liver disease.

Adverse Reactions: Reactions to Marcaine are characteristic of those associated with other amide-type local anesthetics. A major cause of adverse reactions to this group of drugs is excessive plasma levels, which may be due to overdosage, inadvertent intravascular injection, or slow metabolic degradation.

Excessive plasma levels of the amide-type local anesthetics cause systemic reactions involving the central nervous system and the cardiovascular system. The *central nervous system effects* are characterized by excitation or depression. The first manifestation may be nervousness, dizziness, blurred vision, or tremors, followed by drowsiness, convulsions, unconsciousness, and possibly respiratory arrest. Since excitement may be transient or absent, the first manifestation may be drowsiness, sometimes merging into unconsciousness and respiratory arrest. Other central nervous system effects may be nausea, vomiting, chills, constriction of the pupils, or tinnitus. The *cardiovascular manifestations* of excessive plasma levels may include depression of the myocardium, blood pressure changes (usually hypotension), and cardiac arrest. In obstetrics, cases of fetal bradycardia have occurred (see Warnings).

Allergic reactions, which may be due to hypersensitivity, idiosyncrasy, or diminished tolerance, are characterized by cutaneous lesions (e.g., urticaria), edema, and other manifestations of allergy. Detection of sensitivity by skin testing is of doubtful value.

Reactions following epidural or caudal anesthesia also may include: high or total spinal block; urinary retention; fecal incontinence; loss of perineal sensation and sexual function; persistent analgesia, paresthesia, and paralysis of the lower extremities; headache and backache; and slowing of labor and increased incidence of forceps delivery.

Treatment of Reactions. Toxic effects of local anesthetics require symptomatic treatment; there is no specific cure. The physician should be prepared to maintain an airway and to support ventilation with oxygen and assisted or controlled respiration as required. Supportive treatment of the cardiovascular system includes intravenous fluids and, when appropriate, vasopressors (preferably those that stimulate the myocardium). Convulsions may be controlled with oxygen and intravenous administration, in small increments, of a barbiturate, as follows: preferably, an ultrashort-acting barbiturate such as thiopental or thiamylal; if this is not available, a short-acting barbiturate (e.g., secobarbital or pentobarbital) or diazepam. Intravenous barbiturates or anticonvulsant agents should only be administered by those familiar with their use.

References:

1. Ostheimer GW: Obstetrics and local anesthetics: Implications for the fetus and newborn. *Anesthesiology Review* 4:17-23, June 1977.
2. Scanlon JW: Obstetric anesthesia as a neonatal risk factor in normal labor and delivery. *Clinics in Perinatology* 1:465-482, 1974.
3. Scanlon JW, Ostheimer GW, Brown WU, et al: Neurobehavioral responses and drug concentrations in newborns after maternal epidural anesthesia with bupivacaine. *Anesthesiology* 45:400-405, 1976.

BREON LABORATORIES INC.
90 Park Avenue, New York, N.Y. 10016

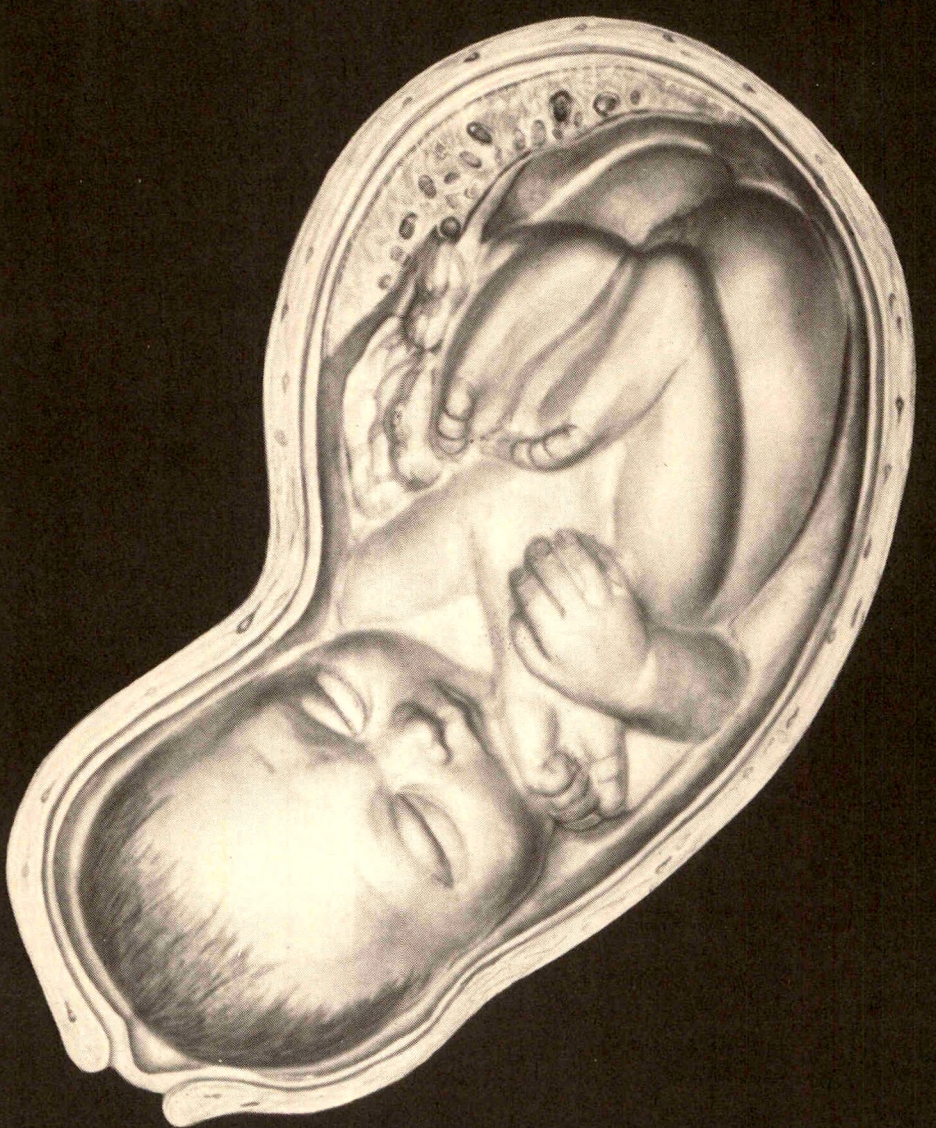
FORMULA

PRODUCT IDENTIFICATION			MULTIPLE DOSE VIAL						SINGLE DOSE AMPUL				
Marcaine HCl (brand of bupivacaine HCl) %	mg./ml.	Epinephrine* (as bitartrate) Dilution	Methyl-paraben mg./ml.	Sodium Bisulfite mg./ml.	Thio-glycerol ml./ml.	Ascorbic Acid mg./ml.	60% Sodium Lactate ml./ml.	Edetate Calcium Disodium mg./ml.	Sodium Bisulfite mg./ml.	Thio-glycerol ml./ml.	Ascorbic Acid mg./ml.	60% Sodium Lactate ml./ml.	Edetate Calcium Disodium mg./ml.
0.25	2.5	—	1	—	—	—	—	—	—	—	—	—	—
0.25	2.5	1:200,000	1	0.5	.001	2	.0017	0.1	.5	.001	2	.0017	0.1
0.5	5.0	—	1	—	—	—	—	—	—	—	—	—	—
0.5	5.0	1:200,000	1	0.5	.001	2	.0017	0.1	.5	.001	2	.0017	0.1
0.75	7.5	—							—	—	—	—	—
0.75	7.5	1:200,000			Not Available in Vials				.5	.001	2	.0017	0.1

Note: The pH of these solutions is adjusted with sodium hydroxide or hydrochloric acid. Sodium chloride has been added to make each solution isotonic.

*Solutions of Marcaine that contain epinephrine should not be autoclaved. Federal law prohibits dispensing without a prescription.

More protection for the newborn



A drug of choice for epidural anesthesia that results in

- decreased placental transfer[1]
- fewer neurobehavioral changes than lidocaine or mepivacaine[2,3]

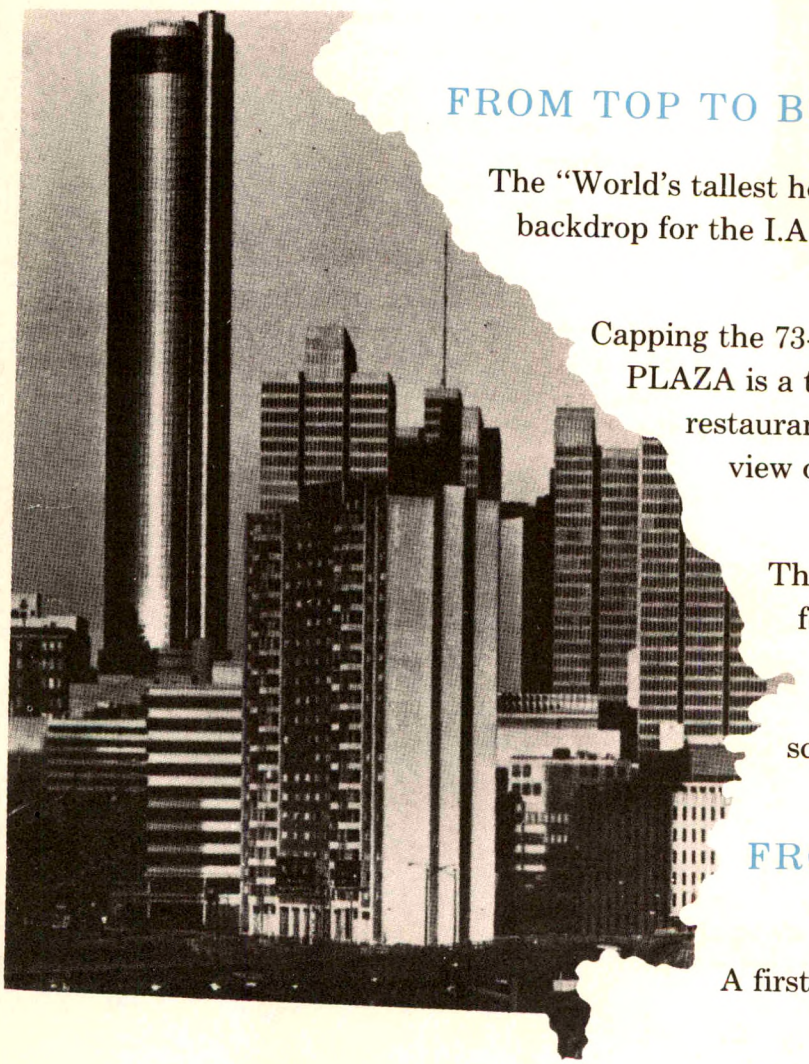
Marcaine® hydrochloride
brand of
bupivacaine hydrochloride
with or without epinephrine 1:200,000

See adjacent page for prescribing information. Not recommended for paracervical block.

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55th Congress — March 8–12, 1981



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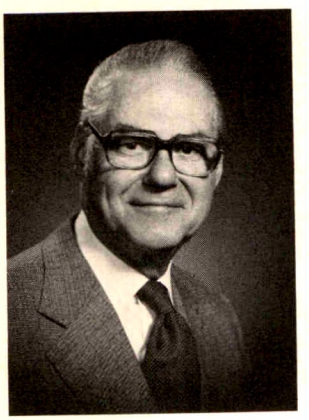
Please see page (22) for program and meeting information.

I.A.R.S. 55th CONGRESS DISTINGUISHED LECTURERS

NINETEENTH ANNUAL BAXTER/TRAVENOL LECTURE

Monday, March 9, 1981

"Health Science Education, Responsibilities and Leadership"



James E. Eckenhoff, M.D., D.Sc
Dean, and Professor of Anesthesia
Northwestern University Medical School
and
President, McGaw Medical Center of
Northwestern University
Chicago, Illinois

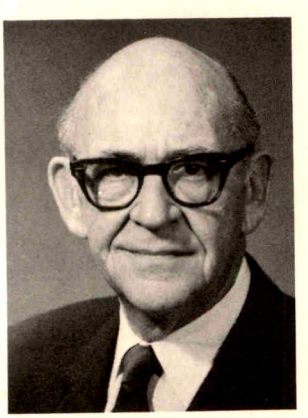
There is probably no one in the specialty better qualified than Doctor Eckenhoff to speak on the subject he has chosen. Distinguished educator and responsible leader, he literally "wrote the book" in anesthesia. To his colleagues throughout the world, he truly needs no further identification.

SIXTEENTH ANNUAL BECTON, DICKINSON AND COMPANY OSCAR SCHWIDETZKY MEMORIAL LECTURE

Tuesday, March 10, 1981

"Voodoo Medicine"

C. Thorpe Ray, M.D.
Professor and Chairman
Department of Medicine
Tulane University School of Medicine
and
Consultant Staff, Ochsner
Foundation Hospital and Touro Infirmary
New Orleans, Louisiana



Notwithstanding his firm dedication to conventional medicine—cardiovascular disease in particular—Doctor Ray's boundless curiosity has led him to explore the medical aspects of the ancient Voodoo religion. Even today, Voodoo medicine is a sorcery to be reckoned with in some parts of the world including the U.S., and as such this authoritative presentation will be of interest to anesthesiologists.

I.A.R.S. 55th CONGRESS—MEETING INFORMATION

SCHEDULE: Sunday, March 8th, 1981

Registration: 2–7 p.m.
Exhibits: 2–5 p.m.
Complimentary Informal Reception: 6–7 p.m.

NOTE: Registration will continue daily throughout the meeting.
Exhibits will continue through Tuesday, March 10th.

SCIENTIFIC PROGRAM: 8:30 a.m. to 5 p.m. Monday, March 9 through Wednesday, March 11
8:30 a.m. to 12 noon on Thursday, March 12th.

.... 66 Scientific papers
.... 15 Review Course Lectures
.... Panel on catastrophic illness
.... Seven "theme" luncheons (tickets to be sold at meeting)
.... Nineteenth Annual Baxter/Travenol Lecture—James E. Eckenhoff, M.D., D.Sc.: "Health Science Education, Responsibilities and Leadership"
.... Sixteenth Annual Becton, Dickinson and Company, Oscar Schwidetzky Memorial Lecture—C. Thorpe Ray, M.D.: "Voodoo Medicine"

PRE-REGISTRATION MATERIAL, HOTEL CARD, DAILY PROGRAM:

Complete meeting information will be mailed by mid-December to all I.A.R.S. members, associate members and educational members.

Non-I.A.R.S. members may receive material by writing or calling the Cleveland business office, 3645 Warrensville Center Rd., Cleveland, Ohio 44122. (216) 295-1124.

NOTE: Abstracts of the 66 scientific papers will be included in the final program booklet distributed at the meeting. A booklet including the 15 Review Course Lectures will be given to meeting attendees as part of their registration. After the meeting, the Review Course Booklet will be available for sale to others through the Cleveland business office.

REGISTRATION FEES:

	Paid by March 2	*Paid at Meeting*
IARS Members and Associate Members	$115	$125
IARS Educational Members	NO FEE	NO FEE
* New IARS Members and Associate Members	$150	$160
** New IARS Educational Members	$35/52	$35/52
Non Members	$165	$175
*** Non Members (residents, nurse trainees)	$ 25	$ 25

* — With membership application, includes dues for one year
** — With membership application, $35 for 2-yr. or $52 for 3-yr. membership
*** — With letter from program director

CONTINUING EDUCATION CREDITS:

American Medical Association: This CME offering meets the criteria for 23 hours of Category 1 credit for the Physicians Recognition Award of the AMA.
American Association of Nurse Anesthetists: Prior approval pending for 23 AANA credits.

EDITORIAL

Cerebral Blood Flow during Cardiopulmonary Resuscitation

Cardiac Output during Cardiopulmonary Resuscitation

Although it is more than two decades since the original description of closed-chest cardiac massage (1), only in the last few years has it become apparent that cardiac output during cardiopulmonary resuscitation (CPR) is not simply a matter of cardiac compression associated with chest compression (2–5). Whereas early work on blood movement during CPR suggested that compression of the heart between the sternum and vertebral column propelled blood from the heart (6, 7), recent studies (2) have documented that myocardial compression is responsible for blood flow in only approximately 20% of patients during CPR. In the remaining patients, external chest compression results in an increase in intrathoracic pressure and an increase in pressure in all the vascular structures in the thorax. This increase in vascular pressure generated by chest compression is transmitted to extrathoracic arteries. In contrast, after an initial retrograde flow, there is obstruction to retrograde flow venous collapse outside the thorax by venous valves, and carotid artery pressure is higher than extrathoracic jugular venous pressure during chest compression. The net result is that during chest compression there is a pressure gradient between arteries and veins outside the thorax that produces the forward flow of blood. When chest compression is released, there is a gradient between the extrathoracic and intrathoracic veins so that flow returns to the heart. Based on this concept Rudikoff et al (4) have demonstrated that maneuvers that increase intrathoracic pressure during CPR increase carotid blood flow. Furthermore, with simultaneous chest compression and positive pressure ventilation ("new" CPR), there is both a higher level of intrathoracic pressure and a higher level of carotid artery blood flow than when positive pressure ventilation occurs between chest compression ("conventional" CPR) (3). Finally, preliminary studies (5) indicate that carotid flow can be further increased by combining synchronized positive pressure ventilation and chest compression with negative pleural pressure between chest compression, increasing venous return.

Supported by National Institutes of Health grant HL 10342.

Carotid Blood Flow vs Cerebral Blood Flow

These studies support the hypothesis that peripheral blood flow in general and carotid arterial blood flow in particular can be maintained during CPR by cyclic changes in intrathoracic pressure. Many investigators (2–5) have recognized, however, that maximizing aortic flow is not sufficient and have concentrated on the distribution of aortic blood flow during CPR. Chandra et al (3) and Rudikoff et al (4) demonstrated a significant increase in carotid flow during CPR in animals with abdominal binding as compared to those without abdominal binding. Unfortunately, the use of carotid blood flow as an index of cerebral blood flow has severe limitations (8, 9), so that it cannot be stated that maneuvers designed to maximize carotid flow (simultaneous ventilation with compression, abdominal binding, etc) actually result in increases in cerebral blood flow. First, blood supply to the brain originates from vessels other than those that arise from the carotid artery (8–10). These vessels include the vertebral arteries that have been shown to be capable of providing adequate cerebral circulation without any flow from the carotid arteries (9). Second, carotid artery blood supplies extracranial (tongue, scalp, cranial muscles) as well as intracranial contents (brain) (10). Third, the spinal anterior arteries supply blood to the brain via channels enclosed in the cord (11). Without direct measurements of cerebral blood flow, increases in carotid blood flow produced by increases in intrathoracic pressure cannot be equated with increases in cerebral blood flow. The principle established with abdominal binding, that a low re-

sistance circuit may receive disproportionately high levels of aortic flow, may apply within the carotid circuit. The low level resistance beds in the tongue and scalp muscles may receive a disproportionate share of carotid blood during CPR. Clearly, blood may be shunted to extracranial sites and not be available for cerebral blood flow. Furthermore, there is reason to be concerned that high levels of positive intrathoracic pressure, as seen during CPR, might theoretically result in decreases in cerebral blood flow.

Effects of CPR on Intracranial Pressure

If the mechanism for blood flow during CPR is related to changes in intrathoracic pressure, it is important to understand how these changes may affect cerebral hemodynamics as this will influence cerebral blood flow during CPR. The relationship between intrathoracic pressure and intracranial pressure (ICP) was first documented in response to positive end-expiratory pressure (PEEP). Both Aidinis (12) and Huseby (13) have shown in dogs without cerebral edema that PEEP may result in increases in ICP. Huseby established a clear relationship between both the changes in pleural pressure and central venous pressure produced by PEEP and the increase in ICP produced by PEEP. On the other hand, Traystman et al (14) have documented that alterations in Pa_{CO_2} produced by PEEP may also play a role in the observed ICP changes. When these experimental observations were repeated in humans, however, the results were not reproducible. Shapiro (15) observed an increase in ICP of greater than 10 torr in only six of 12 patients after application of PEEP and Apuzzo (16) reported similar findings in an additional group of 25 neurosurgical patients.

The potential exists for similar changes in intrathoracic pressure produced by CPR to result in changes in ICP. In fact, Rogers (17) noted in patients with ICP monitoring for head trauma and Reye's syndrome that during CPR there was a direct relationship between chest compression and ICP. These patients had arterial lines and Swan-Ganz catheters in place so that simultaneous pulmonary artery, right atrial, and radial artery pressure could be monitored. During chest compression, as predicted by Chandra et al (3), there was a simultaneous increase in intrathoracic pressure and radial artery pressure. There was a simultaneous increase in ICP so that, in these patients, as radial artery pressure rose during chest compression, so did ICP (17). Because the patients had significant cerebral edema and decreased intracranial compliance, the degree of elevation in ICP was nearly identical with the rise in radial artery pressure. As a result, cerebral perfusion pressure (blood pressure-ICP) remained very low (less than 10 torr) despite an adequate CPR effort as determined by maintenance of an adequate blood pressure.

It remains to be shown that the above data are entirely applicable to adult humans. The observations of Shapiro (15) and of Apuzzo (16), with regard to PEEP and ICP as cited above, showed that PEEP increased ICP in only half the patients, and these patients already had neurologic problems that required ICP monitoring. The two patients observed by Rogers (17) were children, and both had underlying cerebral edema, which may account for the fact that there appeared to be a direct relationship between blood pressure and ICP during CPR. In patients in a normal neurologic state who suffer a sudden cardiac arrest, it is not clear as to the extent that these same changes in ICP will occur or that these changes will be associated with deleterious effects on cerebral blood flow. Regardless, it is important to recognize that increasing intrathoracic pressure can be associated with both increasing ICP and with increasing carotid artery pressure during CPR. As a result, cerebral perfusion pressure during CPR will be determined by the difference in effect of increasing intrathoracic pressure on ICP and on systemic pressure. There may be a point at which increases in intrathoracic pressure designed to increase carotid artery pressure may actually result in a greater increase in ICP than a systemic pressure with a consequent decrease in cerebral blood flow. It is clear that this point will vary depending on the intracranial compliance at the start of chest compression and that intrathoracic pressure changes during chest compression must be analyzed for their effects on intracranial hemodynamics as well as on systemic blood pressure and carotid flow.

Effects of CPR on Cerebral Blood Flow

There is a clear need to find improved methods of CPR that will result in improved cerebral blood flow. The generally poor outcome observed for survivors of prolonged (more than 10 minutes) conventional CPR largely appears to be related to profound neurologic damage suffered during prolonged CPR (18). Furthermore, there are few published experimental studies measuring cerebral blood flow during CPR and the studies that have been published have tech-

nical features which make their interpretation different (19). These technical features include the need to validate the use of microsphere techniques under the very low flow and poor mixing conditions of CPR. Other techniques of cerebral blood flow measurement, such as the cerebral venous outflow technique, disrupt venous drainage connections to the chest and interfere with the transmission of pleural pressure into the intracranial vault.

We have recently conducted a series of experiments in which we have validated our microsphere measurements of cerebral blood flow with thallium measurements in order to evaluate critically cerebral blood flow during CPR. It appears that the technique can be used with certain precautions, particularly at the very low flow rates seen during ineffective conventional CPR. We are now comparing direct measurements of cerebral blood flow with different CPR techniques in order to determine which methods result in acceptable levels of cerebral blood flow. We are also investigating the mechanism by which pleural pressure changes result in changes in ICP in order to understand how best to increase intrathoracic pressure without increasing ICP and lowering cerebral perfusion pressure. Finally, we are trying to determine which, if any, patient populations, in addition to children with brain edema, might require attention to these physiologic relationships.

Conclusion

It is not yet clear which CPR techniques will result in maximum cerebral blood flow. In addition to the specific techniques of chest compression and ventilation, much information remains to be discovered about the role of osmotic diuretics, lowered P_{aCO_2}, vasoconstrictors to raise arterial pressure, and similar maneuvers on maximizing cerebral blood flow during CPR. The exact recommendations may be different for infants versus adults and for patients with preexisting cerebral edema versus those with normal neurologic states. It is clear, however, that the physiologic relationships between intrathoracic pressure, pleural pressure, venous pressure, intracranial pressure, and cerebral blood flow represented by these investigations into CPR serve as the next steps in modifying current CPR techniques and will result in better neurologic recovery following cardiac arrest.

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REFERENCES

1. Kouwen-Loven WB, Jude JR, Knickerbocker GG. Closed chest cardiac massage. JAMA 1970;173:1064–7.
2. Taylor GJ, Tucker WM, Greene HL, et al. Medical intelligence—the importance of prolonged compression during cardiopulmonary resuscitation in man. N Engl J Med 1977;296: 1515–7.
3. Chandra N, Rudikoff M, Weisfeldt ML. Simultaneous chest compression and ventilation at high airway pressure during cardiopulmonary resuscitation. Lancet 1980;1:175–8.
4. Rudikoff MT, Maughan WL, Effron M, et al. Mechanism of blood flow during cardiopulmonary resuscitation. Circulation 1980;61:345–52.
5. Chandra N, Cohen JM, Tsitlick J, et al. Negative airway pressure between compressions augments carotid flow during CPR. Circulation 1979;60(II):46.
6. Safar P, Brown TC, Hottey WJ, Wilder RJ. Ventilation and circulation with closed chest cardiac massage in man. JAMA 1961;176:574–6.
7. Harris L, Kirimli B, Safar P. Augmentation of artificial circulation during cardiopulmonary resuscitation. Anesthesiology 1967;28:730–4.
8. Traystman RJ, Rapela CE. Effect of sympathetic nerve stimulation on cerebral and cephalic blood flow in dogs. Circ Res 1975;36:620–30.
9. Rapela CE, Green HD. Autoregulation of canine cerebral blood flow. Circ Res 1964;15:205–11.
10. Norcross ND. Intracranial blood flow. Arch Neurol Psychiat 1938;40:291–9.
11. Betz E. Cerebral blood flow: its measurement and regulation. Physiol Rev 1972;52:595–618.
12. Aidinis SJ, Lafferty J, Shapiro HM. Intracranial pressure responses to PEEP. Anesthesiology 1976;45:275–86.
13. Huseby JS, Pavlin EG, Bulter J. Effect of positive end-expiratory pressure on intracranial pressure in dogs. J Appl Physiol 1978;44:25–7.
14. Traystman RJ, Rogers MC, Stidham GL. The effect of positive end-expiratory pressure on intracranial pressure and cerebral blood flow. Circulation 1980;62(III):134.
15. Shapiro HM, Marshall LF. Intracranial pressure responses to PEEP in head-injured patients. J Trauma 1978;18:254–6.
16. Apuzzo MLJ, Weiss MH, Petersons V, et al. Effects of positive end-expiratory ventilation on intracranial pressure in man. J Neurosurg 1977;46:227–32.
17. Rogers MC, Nugent SK, Stidham G, et al. Effects of closed-chest cardiac massage on intracranial pressure. Crit Care Med 1979;7:454–6.
18. Weale FE, Rothwell, Jackson RL. The efficiency of cardiac massage. Lancet 1962;1:990–2.
19. Voorhees WD, Babbs CF, Tacker WA, Jr. Regional blood flow during cardiopulmonary resuscitation in dogs. Crit Care Med 1980;8:134–6.

ANESTH ANALG
60:76-80, 1981

Early Extubation versus Prophylactic Ventilation in the High Risk Patient: A Comparison of Postoperative Management in the Prevention of Respiratory Complications

Lt Comdr Steven R. Shackford, MC, USN,* Richard W. Virgilio, MD, FACS,* and Richard M. Peters, MD, FACS†

SHACKFORD, S. R., VIRGILIO, R. W., AND PETERS, R. M.: Early extubation versus prophylactic ventilation in the high risk patient: a comparison of postoperative management in the prevention of respiratory complications. Anesth Analg 1981;60:76-80.

To evaluate whether prophylactic ventilation during the early postoperative period diminishes pulmonary complications, 35 high risk, elderly patients undergoing major, elective abdominal aortic reconstruction were prospectively randomized into either an early extubation group or a prophylactic ventilation group. The 17 patients assigned to the prophylactic ventilation group received mechanical ventilation by assist/control mode until 8 a.m. of the first postoperative day. The 17 patients assigned to the early extubation group were extubated after the operation as soon as they could maintain a pH of 7.35, with a spontaneous respiratory rate of less than 30. Preoperative measurements of functional residual capacity, intrapulmonary shunt, and oxygen delivery were compared to similar measurements during the initial two postoperative days. There were no significant differences between the groups with respect to age, length of operation, duration of anesthesia, operative blood loss, intraoperative fluid administration, or number of intraoperative transfusions. Patients in the prophylactic ventilation group were ventilated for an average of 18.3 ± 0.5 hours. Patients in the early extubation group were ventilated for an average of 3.3 ± 0.5 hours ($p < 0.0005$). No patient in either group required reintubation. Intrapulmonary shunt and oxygen delivery were not significantly different between the groups at any time during the study period. There was no mortality or significant morbidity in either group. These findings suggest that in high risk surgical patients, prophylactic ventilation, per se, may not diminish respiratory complications or improve gas exchange.

Key Words: VENTILATION: artificial; INTUBATION: duration.

ELDERLY PATIENTS undergoing major abdominal surgery under general anesthesia are at increased risk of developing significant postoperative respiratory complications. It has been suggested that the frequency and severity of these respiratory complications can be reduced by extending the duration of respiratory support into the postoperative period (1). For this reason, many institutions employ routine prophylactic intubation and mechanical ventilation for the high risk patient in the early postoperative period. Although this practice is common, its efficacy in preventing postoperative complications has not been documented. To evaluate this form of respiratory support, we prospectively compared overnight prophylactic ventilation to early postoperative extubation in high risk patients undergoing major, elective aortic reconstructive surgery.

Methods and Materials

From April 1978 to May 1979, all patients admitted to the peripheral vascular service of the Naval Re-

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Supported by the Office of Naval Research Contract N00014-76-C-0282 and by United States Public Health Service grants GM 17284 and HL 13172.

Received from the Trauma Research Unit, Naval Regional Medical Center, San Diego, California, and the Division of Thoracic Surgery, University of California, San Diego, California. Accepted for publication October 25, 1980.

The opinions or assertions expressed herein are those of the authors and are not to be construed as official or as reflecting the views of the Navy Department or the Naval Service at large.

Reprint requests to Dr. Shackford, Trauma Research Unit, Naval Regional Medical Center, San Diego, CA 92134.

gional Medical Center, San Diego for elective aortic reconstruction were eligible for the study. After informed consent was obtained patients were assigned by random number to one of two groups: prophylactic ventilation (PV) or early extubation (EE). Before the operation, peripheral arterial and #7 French thermistor-tipped, quadruple-lumen, flow-directed pulmonary arterial catheters (Edwards Laboratory, Santa Ana, CA) were inserted. The following measurements and calculations were made before surgery, during surgery, and daily for 2 days after surgery: pulmonary capillary wedge pressure (PCWP); cardiac output by thermal dilution; arterial and mixed venous blood gas tensions, and pH while the patient was breathing an inspired oxygen fraction (F_{IO_2}) of 0.45; intrapulmonary shunt ($\dot{Q}s/\dot{Q}t$) by the Berggren equation (2); arterial and mixed venous oxygen content; and oxygen delivery. Oxygen delivery was calculated from the arterial oxygen content and the cardiac output. In the last 15 patients admitted to the study, functional residual capacity (FRC) was measured with the patient in the semirecumbent position before surgery, before extubation, and at discharge from the intensive care unit using the helium rebreathing method described by Heldt and Peters (3). Standard portable posterior-anterior view chest x-rays were obtained before surgery, immediately after surgery, and daily for 2 days. In all cases, the anesthetic was administered by the same team of anesthesiologists, the operation performed by the same surgical team, and the postoperative care administered by the same nursing staff. Neither the anesthesiologist nor the surgeon was informed as to the mode of postoperative ventilator management that would be used. Premedication uniformly consisted of intramuscular morphine sulfate or oral diazepam given before transportation to the operating room. In all cases, a balanced anesthetic technique of nitrous oxide supplemented with narcotic analgesics and muscle relaxants was used. The effects of the muscle relaxants were not antagonized pharmacologically at the termination of the anesthesia. All procedures were performed through a standard midline incision extending from the epigastrium to the pubis. Intraoperative blood loss was replaced with packed red blood cells reconstituted with normal saline. Additional crystalloid was given to maintain the pulmonary capillary wedge pressure within 3 torr of preoperative values. After surgery, all patients were transferred, awake and alert, to the Shock and Trauma Research Unit, an intensive care area.

Patients assigned to the PV group received mechanical ventilation with the Bennett MA-1 volume cycled ventilator (Bennett Respiration Products, Santa Monica, CA) by assist/control mode until 8 a.m. of the first postoperative day. The delivered tidal volume was 15 ml/kg. With a minimum inspiratory effort (−2 cm H_2O), patients received a ventilator breath. A back-up rate of six ventilator breaths per minute was delivered to patients who were apneic. At 8 a.m., the patients were placed on a "T" adapter blow-by system delivering a measured F_{IO_2} of 0.45 or greater, if needed. If, after 30 minutes, oxygenation and ventilation were adequate as judged by blood gas analysis and if the spontaneous respiratory rate was less than 30, the orotracheal tube was removed. If arterial blood gas tensions had deteriorated and the spontaneous rate exceeded 30, the patient was maintained on the ventilator.

Patients assigned to the EE group were given intermittent mandatory ventilation immediately after surgery. This consisted of a Bennett MA-1 ventilator modified to allow unassisted and unrestricted spontaneous breaths to occur between mechanical breaths. The ventilator initially delivered six mechanical breaths with a tidal volume set at 15 ml/kg. If, after 30 minutes, the patient maintained a pH of greater than 7.35 with a spontaneous respiratory rate of less than 30, the mechanical rate was decreased to three and arterial blood gas tensions were measured again after 30 minutes. If the pH and spontaneous rate were maintained, the mechanical rate was then decreased to zero and the blood gas tensions were again determined after 30 minutes. If the pH and the rate criteria were met, the patient was extubated.

Postoperative medications for analgesia and sedation consisted of morphine sulfate and diazepam administered intravenously. The amount of medication administered was titrated to each patient's need for sedation and for control of pain as judged by the nursing staff.

Groups were compared with respect to the following variables: American Society of Anesthesiologists' Classification of Physical Status (4); $\dot{Q}s/\dot{Q}t$; oxygen delivery; FRC; P_{aCO_2}; duration of anesthesia and operation; operative blood loss; fluid and blood administration; duration of mechanical ventilation; magnitude of analgesic requirements; respiratory complications; and duration of stay in the intensive care unit. Major respiratory complications were felt to occur if the patient developed lobar atelectasis, pneumonia, or frank respiratory failure manifested by a need for continued mechanical ventilation or re-intubation and mecchanical ventilation. Discoid atelectasis seen on a chest x-ray, which responded to chest physiotherapy,

was felt to be a minor complication. Contrasts were sought using the Student's *t*-test. Statistical significance was attributed to a *p* value of less than 0.01.

Results

Of the 35 patients (30 men and five women) eligible for the study, none declined to enter the study and none were eliminated. Eighteen patients (13 men and 5 women) were randomized to the PV group and 17 patients (all men) to the EE group. The groups were well matched with regard to operative risk as evidenced by age, associated systemic diseases, smoking history, and the American Society of Anesthesiologists' Classification of Physical Status (Table 1). The groups were also similar with respect to all preoperative measurements and calculations (Table 2); there was no statistical difference between the groups with regard to any of the parameters. Specifically, the groups had similar lung function as measured by $\dot{Q}s/\dot{Q}t$ and FRC, and similar cardiac function as measured by cardiac index. Five aortic aneurysmectomies, 11 aortobifemoral bypasses, and two renal artery reconstructions were performed in the PV group, whereas 12 aortic aneurysmectomies and five aortobifemoral bypasses were performed in the EE group. There were no significant differences between the groups with respect to the duration of operation or anesthesia, operative blood loss, intraoperative transfusions, and intraoperative fluid requirement (Table 3).

Duration of postoperative mechanical ventilation was 18.3 ± 0.5 hours in the PV group and 3.3 ± 0.5 hours in the EE group. No patient in either group required re-intubation. The difference between the groups with respect to duration of postoperative intubation and mechanical ventilation was statistically significant (Table 4).

Patients in the PV group required significantly more morphine sulfate and diazepam than patients in the EE group (Table 4).

There were no statistically significant differences between the groups in postoperative $\dot{Q}s/\dot{Q}t$ at any time during the study period (Table 5). Oxygen delivery in the postoperative period was appropriately elevated in both groups over preoperative values, but was not significantly different between groups at any time during the postoperative period (Table 5). As expected, postoperative FRC decreased significantly

TABLE 1
Associated Systemic Disease

	Group	
	Prophylactic overnight ventilation	Early postoperative extubation
Age (mean years ± SEM)	59 ± 2	62 ± 2
Patients with a history of:		
Myocardial infarction	1	2
Congestive heart failure	2	0
Chronic lung disease	1	2
Chronic cardiac arrhythmia	2	3
Smoking (pack years*) (mean ± SEM)	55 ± 5	66 ± 6
A.S.A.† (mean ± SEM)	2.8 ± 0.2	2.7 ± 0.1

* Pack years are determined by multiplying the packs of cigarettes smoked per day by the number of years the patient has smoked.
† American Society of Anesthesiologists' classification of physical status: 2, patient with mild systemic disease; 3, patient with a severe systemic disease that limits activity.

TABLE 2
Preoperative Comparisons*

	Group	
	Prophylactic overnight ventilation	Early postoperative extubation
Pa_{O_2} (torr)	72 ± 2	71 ± 2
Pa_{CO_2} (torr)	37 ± 4	36 ± 4
Cardiac index (L/min/m²)	3.1 ± 0.1	3.2 ± 0.1
O_2 delivery (ml/min)	1035 ± 64	1077 ± 41
PCWP (torr)	9 ± 3	7 ± 3
$\dot{Q}s/\dot{Q}t$ (%)	12.0 ± 0.8	11.3 ± 0.6
FRC (ml)	3242 ± 665	3626 ± 165

* Values are means ± SEM.

TABLE 3
Intraoperative Comparison*

	Group	
	Prophylactic overnight ventilation	Early postoperative extubation
Duration of anesthesia (hr)	5.9 ± 0.5	5.2 ± 0.3
Duration of operation (hr)	5.2 ± 0.5	4.5 ± 0.3
Blood loss (ml)	3911 ± 697	2990 ± 180
Transfusions (units)	7.7 ± 1.4	5.5 ± 0.4
Fluids (ml)	8588 ± 1291	7217 ± 368

* Values are means ± SEM.

TABLE 4
Postoperative Comparison*

	Group		
	Prophylactic overnight ventilation	Early postoperative extubation	*p* value
Duration of mechanical ventilation (hr)	18.3 ± 0.5	3.3 ± 0.5	<0.0005
Morphine sulfate (mg)†	45 ± 9	12 ± 6	<0.0025
Diazepam (mg)†	22 ± 6	4 ± 2	<0.005
Duration of ICU stay (days)	2.9 ± 0.2	2.3 ± 0.1	NS

* Values are means ± SEM.
† Administered from end of operation until 8 a.m. of 1st postoperative day.

TABLE 5
Postoperative Comparisons*

Parameters	Day of operation	Pre-extubation	1st postoperative day	2nd postoperative day
$\dot{Q}s/\dot{Q}t$ (%)				
PV group	15.6 ± 0.9		18.2 ± 1.6	18.6 ± 1.6
EE group	14.2 ± 0.9		15.9 ± 1.2	15.9 ± 1.6
O_2 delivery (ml/min)				
PV group	1265 ± 108		1426 ± 82	1205 ± 92
EE group	1324 ± 118		1360 ± 63	1404 ± 61
Pa_{CO_2} (torr)				
PV group		38 ± 0.9	38 ± 1.0	40 ± 1.2
EE group		40 ± 0.6	40 ± 0.7	39 ± 0.8
FRC (ml)				
PV group		1768 ± 164	2120 ± 450	2893 ± 364
EE group		2122 ± 199	3162 ± 217	3480 ± 182

* Values are means ± SEM.

from preoperative values in both groups (Table 5). Before extubation, mean FRC in the PV group decreased 45%, whereas mean FRC in the EE group decreased 41% in the perioperative period. FRC was measured on the first postoperative day after the patients in the EE group had been extubated for a mean of 17 ± 1 hours and, in patients in the PV group, 3 ± 0.1 hours following extubation.

No patient in either group was hypocapneic at any time during the study period (Table 5). The average respiratory rate immediately after extubation was 24 ± 1 breaths per minute in the PV group and 20 ± 1 breaths per minute in the EE group. Only one patient (PV group) had a respiratory rate of 30 after extubation.

None of the patients in either group developed a major respiratory complication. Discoid atelectasis appeared on chest x-ray in two patients in the PV group and in three patients in the EE group. In all patients, this responded to chest physiotherapy and vigorous pulmonary toilet within 24 hours. Duration of stay in the intensive care unit was 2.9 ± 0.2 days for the PV group and 2.3 ± 0.1 days for the EE group. There was no mortality or significant morbidity in either group.

Discussion

Pulmonary complications are the major cause of morbidity and mortality in the postoperative period (5). These occur in up to 40% of patients undergoing abdominal surgery (6–8). Among patients felt to be at an increased risk of developing postoperative pulmonary complications are the elderly, men, those having operations lasting longer than 4 hours, those receiving intraoperative transfusion of more than 4 units of blood, and those having an incision on the upper abdomen (1, 9–11).

The cause of postoperative pulmonary morbidity is complex. Splinting and shallow respirations brought about by incisional pain cause alveolar and small airway collapse (microatelectasis). This leads to changes in the ventilation-perfusion ratio in all areas of the lung, causing an increase in intrapulmonary shunt and hypoxemia. Atelectasis also alters the mechanical properties of the lung causing a decrease in pulmonary compliance that increases the work of breathing, further contributing to the hypoxemia (12).

Changes such as those described are also seen in anesthetized patients, but can be prevented by periodic deep breaths (13). Therefore, some authors (14) have reasoned that alveolar collapse can be prevented in the postoperative period by use of intermittent positive pressure breathing. Others (15–19) do not agree and the evidence does not support the use of intermittent positive pressure breathing in the postoperative patient (20). Schmidt et al (1) have advocated prophylactic intubation and continuous positive airway pressure to prevent airway collapse and subsequent respiratory failure in the high risk patient. Many surgeons and anesthesiologists now routinely use prophylactic ventilation during the first 12 to 20 postoperative hours in patients at increased risk for development of postoperative respiratory complications or failure. The impetus for use of prophylactic mechanical ventilation comes from the experience with patients undergoing cardiac procedures utilizing cardiopulmonary bypass (21). Although prophylactic mechanical ventilation has become routine in many institutions for the postoperative management of patients having open heart surgery, there are disadvantages. Among these are the risks of barotrauma and/or nosocomial infection, the need for more invasive monitoring, increased medication required for sedation, the risk of endotracheal tube occlusion, possible ventilation alarm fault, and increased cost. Because of the risks and disadvantages associated with this type of postoperative ventilator management, several authors (22–24) have advocated selective early extubation of the cardiac patient in the postoperative period. A similar study would be helpful to learn whether our findings also apply to cardiac surgery patients.

In our study, routine prophylactic ventilation of high risk surgical patients undergoing laparotomy for vascular disease did not improve respiratory function or decrease the incidence of respiratory complications. We were unable to demonstrate that postoper-

ative prophylactic ventilation improved oxygen delivery, intrapulmonary shunt, functional residual capacity, or incidence of major pulmonary complications when compared to early extubation. In fact, the improvement in FRC seen in the EE group on the first postoperative day suggests to us that earlier extubation results in earlier normalization of the FRC.

There is no doubt that mechanical ventilation is indicated in patients with respiratory failure due to inadequate alveolar ventilation. Similarly, deteriorating lung function manifested by an inability to oxygenate and a decrease in the FRC is best treated by continuous positive airway pressure. The success of mechanical ventilation and continuous positive airway pressure in these situations is unquestioned. This success, however, does not justify the routine prophylactive use of intubation and mechanical ventilation in the high risk surgical patient when neither defect is present.

REFERENCES

1. Schmidt GB, O'Neill WW, Kotb K, Hwang KK, Bennett EJ, Bombeck CT. Continuous positive airway pressure in the prophylaxis of the adult respiratory distress syndrome. Surg Gynecol Obstet 1976;143:613–8.
2. Berggren SM. The oxygen deficity of arterial blood caused by nonventilating parts of the lung. Acta Physiol Scand 1942 (Suppl 1):1.
3. Heldt GP, Peters RM. A simplified method to determine functional residual capacity during mechanical ventilation. Chest 1978;74:492–6.
4. New classification of physical status. Anesthesiology 1963;24: 111.
5. Moore FD, Lyons JH, Pierce EC, et al. Post-traumatic pulmonary insufficiency. Philadelphia: WB Saunders, 1969:3.
6. Anscombe AR. Pulmonary complications of abdominal surgery. Chicago: Year Book Medical Publishers, 1957:7.
7. Latimer RG, Dickman M, Day WC, Gunn ML, Schmidt CD. Ventilatory patterns and pulmonary complications after upper abdominal surgery determined by preoperative and postoperative computerized spirometry and blood gas analysis. Am J Surg 1971;122:622–32.
8. Bartlett RH, Gazzaniga AB, Geraghty TR. Respiratory maneuvers to prevent postoperative pulmonary complications: a critical review. JAMA 1973;224:1017–21.
9. Szauer JS, Zukaukas C: The problems of abdominal operations in elderly patients. Geriatrics 1975;30:57–9, 63–4.
10. Hamilton WK: Atelectasis, pneumothorax, and aspiration as postoperative complications. Anesthesiology 1961;22:708–22.
11. Dripps RD, Van Deming M. Postoperative atelectasis and pneumonia. Ann Surg 1946;124:94–110.
12. Peters RM. Work of breathing following trauma. J Trauma 1968;8:915–23.
13. Bendixen HH, Hedley-Whyte J, Chir B, Laver MB. Impaired oxygenation in surgical patients during general anesthesia with controlled ventilation: a concept of atelectasis. N Engl J Med 1963;269:991–6.
14. Anderson WH, Dossett BE Jr, Hamilton GL. Prevention of postoperative pulmonary complications. JAMA 1963;6:763–6.
15. Barach AL, Segal MS. The indiscriminate use of IPPB. JAMA 1975;231:1141–2.
16. Baxter WE, Levine RS. An evaluation of IPPB in the prevention of postoperative pulmonary complications. Arch Surg 1969;8: 795–8.
17. Cottrell JE, Siker ES. Preoperative intermittent positive pressure breathing therapy in patients with chronic obstructive lung disease: effect on postoperative pulmonary complications. Anesth Analg 1973;52:258–62.
18. Petty TL. A critical look at IPPB. Chest 1974;66:1–3.
19. McConnell DH, Maloney JV Jr, Buckberg GD. Postoperative intermittent positive pressure breathing treatments. J Thorac Cardiovasc Surg 1974;8:944–52.
20. Gold MI. Is intermittent positive pressure breathing therapy (IPPB Rx) necessary in the surgical patient? Ann Surg 1976;4: 122–3.
21. Lefemine AA, Harken DE. Postoperative care following open-heart operations: routine use of controlled ventilation. J Thorac Cardiovasc Surg 1966;52:207–16.
22. Prakash O, Jonson B, Meij S, et al. Criteria for early extubation after intracardiac surgery in adults. Anesth Analg 1977;56:703–8.
23. Klineberg PL, Geer RT, Hirsh RA, Aukburg SJ. Early extubation after coronary artery bypass graft surgery. Crit Care Med 1977;5:272–4.
24. Barash PG, Lescovich R, Katz JD, Talner NS, Stansel HC Jr. Early extubation following pediatric cardiothoracic operation: a viable alternative. Ann Thorac Surg 1980;29:228–33.

ANESTH ANALG
60:81-84, 1981

Failure of Naloxone to Reverse Analgesia from Transcutaneous Electrical Stimulation in Patients with Chronic Pain

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ABRAM, S. E., REYNOLDS, A. C., AND CUSICK, J. F.: Failure of naloxone to reverse analgesia from transcutaneous electrical stimulation in patients with chronic pain. Anesth Analg 1981;60:81-84.

To investigate the possible role of endogenous opiates in the mediation of analgesia produced by low intensity, high frequency transcutaneous electrical stimulation in the presence of chronic pain, an attempt was made to reverse stimulation-induced analgesia with naloxone. Fifteen patients with chronic pain who were consistently relieved of pain by low intensity, high frequency transcutaneous stimulation were studied. During stimulation at 58 Hz, patients were given double-blind intravenous injections of either naloxone (0.4 or 1.2 mg) or saline. Subjective pain ratings were recorded before stimulation, after stimulation, and after naloxone and saline injections. No reversal of analgesia was seen after naloxone or saline. These results suggest that transcutaneous stimulation at low intensity and high frequency may provide analgesia that is not associated with release of endogenous opiates in patients with chronic pain.

Key Words: NERVE, stimulator, transcutaneous; BRAIN, endorphin; PAIN, chronic.

LOW INTENSITY, high frequency transcutaneous electrical stimulation has been used to produce analgesia in both acute and chronic pain states. The mechanism by which it reduces pain perception is not yet clear. One mechanism, which has been considered recently, involves activation or release of endogenous opiates.

Chapman and Benedetti (1), and Sjölund and Eriksson (2) found that analgesia induced by high intensity, low frequency transcutaneous electrical stimulation is at least partially reversed by relatively low doses of naloxone (0.4 to 1.6 mg). Likewise, reversal of electroacupuncture analgesia by a narcotic antagonist has also been reported (3). Thus it appears that high intensity peripheral stimulation is capable of activating pain-controlling mechanisms mediated by endogenous opiates. On the other hand, Woolf et al (4) have demonstrated the failure of naloxone to reverse the analgesia induced by low intensity, high frequency transcutaneous stimulation when used for relief of acute pain associated with rib fractures.

This study was undertaken to determine whether analgesia induced by conventional high frequency, low intensity transcutaneous stimulation for relief of chronic pain may involve endogenous opiates.

Methods

Fifteen patients with chronic pain of nonmalignant origin who had been using transcutaneous electrical stimulation successfully for at least 1 month were chosen for this study. None was taking narcotic analgesics. Sites of pain and presumptive diagnoses are listed in Table 1.

After obtaining informed consent, the first 10 patients were given transcutaneous stimulation on two occasions at sites they had previously been using. Electrical stimulation was performed using a Medtronic (Neuromod) model 3722 dual-channel stimulator and standard carbonrubber electrodes (Medtronic, Inc., Minneapolis, MN). Pulse width was held constant at 320 μsec, and frequency was set at 58 Hz. The current amplitude was set by the patient to the intensity routinely used to produce analgesia, generally just below threshold for discomfort or motor stimulation (about 12 to 20 mamp peak current at impedances of 1,200 to 1,300 ohm). Subjective pain

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Financial support provided by Medtronic, Inc.
Received from the Departments of Anesthesiology and Neurosurgery, The Medical College of Wisconsin, 8700 West Wisconsin Avenue, Milwaukee, Wisconsin 53226. Accepted for publication October 30, 1980.
Reprint requests to Dr. Abram.

TABLE 1
Age, Sex, Location of Pain, and Presumptive Diagnosis in Study Patients

Patient	Age (yr)	Sex	Pain		Diagnosis
			Site	Duration	
1	39	M	Calf, ankle	5 yr	Sympathetic dystrophy
2	27	M	Low and mid-back	12 mo	Myofascial syndrome
3	30	F	Foot, ankle	10 yr	Lumbar radiculopathy
4	39	M	Hand	3 yr	Sympathetic dystrophy
5	39	M	Foot	9 mo	Sympathetic dystrophy
6	54	M	Back, thigh	7 yr	Lumbar radiculopathy
7	28	F	Arm, shoulder	12 mo	Myofascial syndrome
8	37	F	Low and mid-back	3 yr	Myofascial syndrome
9	50	M	Neck, shoulders	7 mo	Myofascial syndrome
10	43	F	Low back	2 mo	Myofascial syndrome
11	50	F	Low back, leg	5 yr	Lumbar radiculopathy
12	32	F	Upper back, shoulder	7 mo	Myofascial syndrome
13	61	F	Anterior chest wall	16 mo	Costal chondritis
14	27	F	Mid-back	2 yr	Incisional pain
15	47	F	Upper back, shoulders	2 yr	Myofascial syndrome

ratings were made using a visual 1 to 10 scale (Fig. 1) before stimulation and after achieving analgesia, at least 20 minutes after stimulation was begun. With stimulation still applied, either saline, 1 ml, or naloxone, 0.4 mg, selected in a random, double-blind fashion, was injected intravenously. Patients were told that the injection might enhance or diminish pain relief afforded by electrical stimulation. Pain ratings were again reported 10 and 20 minutes after injection, while stimulation was continued. Stimulation was then stopped and, 5 minutes later, another pain rating was recorded. Patients returned on another day, and the protocol was repeated, injecting the opposite medication (naloxone or saline).

In order to assess the possibility that, naloxone 0.4 mg, might be insufficient to reverse endogenous opiate effects, an additional five patients were studied in an identical manner using naloxone, 1.2 mg, and normal saline, 3 ml.

Pain ratings before injection of saline were compared to ratings before naloxone by paired *t*-test to assess the adequacy of randomization. Comparisons of pain ratings after injections, as well as changes from poststimulation preinjection ratings to postinjection ratings for saline vs naloxone, were also analyzed by paired *t*-test.

This study was approved by the Human Research Review Committees of the Milwaukee County Medical Complex and The Medical College of Wisconsin.

Results

In all patients pain ratings decreased during stimulation. In 14 patients, pain ratings remained the same

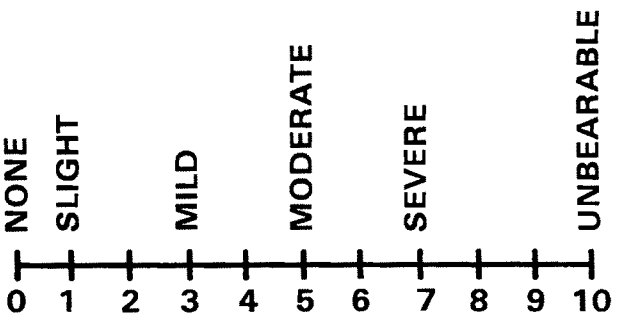


FIG 1. Subjective pain rating scale.

or decreased further after both saline and naloxone injections (Table 2). In one patient, the pain rating increased from 1 to 3 over 20 minutes after naloxone, 1.2 mg; an identical increase was also seen after saline. The change in pain ratings was not statistically different after injection of naloxone than it was after saline for both the low dose and high dose groups. Mean pain ratings for saline and naloxone trials are shown in Figs 2 and 3.

Discussion

Failure of naloxone to diminish the analgesia produced by conventional low intensity, high frequency transcutaneous electrical stimulation in patients with chronic pain suggests the possibility that this type of analgesia may not be associated with release of endogenous opiates. Our results agree with those of Sjölund and Eriksson (5), who reported similar results when naloxone was given to chronic pain patients receiving conventional transcutaneous stimulation; however, they found that naloxone reversed analgesia

TABLE 2

Pain Ratings during Electrical Stimulation Before and After Nalaxone or Saline*

Patient	Naloxone					Saline				
	Prestimulation	During stimulation			Poststimulation: 25 min after injection	Prestimulation	During stimulation			Poststimulation: 25 min after injection
		Preinjection	10 min after injection	20 min after injection			Preinjection	10 min after injection	20 min after injection	
1	6	5	4	3	2	6	4	3	2	1
2	6	4	3	2	2	6	4	3	3	2
3	8	4	3	3	3	9	8	6	6	5
4	3	2	1	0	0	2	0	0	0	0
5	5	3	3	2	2	6	4	3	2	3
6	3	2	1	1	1	4	2	2	2	2
7	6	3	2	3	2	5	3	2	2	2
8	5	4	3	3	3	4	3	3	3	3
9	8	5	3	1	1	8	6	3	1	2
10	5	3	2	1	0	4	2	2	2	0
11	9	2	1	0	0	4	0	0	0	0
12	6	4	2	2	0	6	4	2	2	2
13	4	2	1	0	0	6	3	2	1	1
14	5	1	2	3	2	5	1	2	3	2
15	8	5	4	4	4	5	2	1	1	0

* Patients 1 to 10 received naloxone, 0.4 mg, and saline; patients 11 to 15 received naloxone, 1.2 mg, and saline. See Fig 1 for pain ratings.

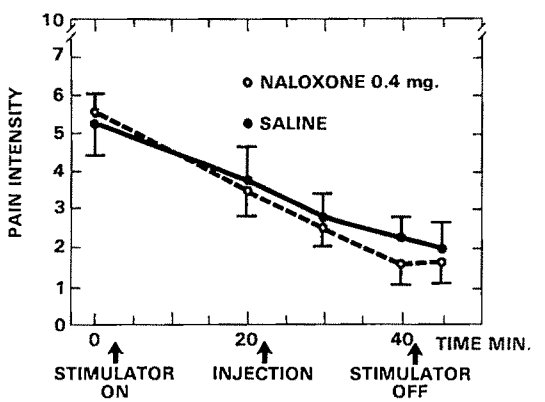


FIG 2. Mean pain ratings during transcutaneous electrical stimulation in 10 patients who received saline on one trial and naloxone, 0.4 mg, on the other trial. Vertical bars represent SEM.

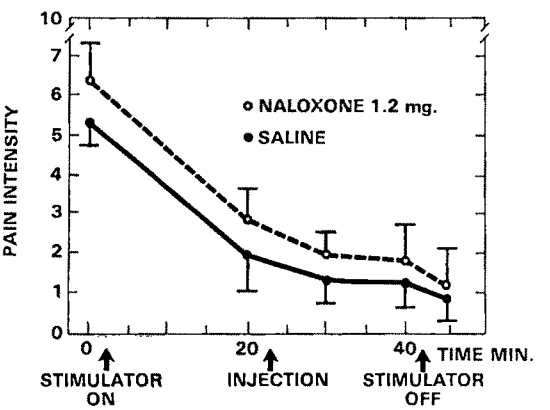


FIG 3. Mean pain ratings during transcutaneous electrical stimulation in five patients who received saline on one trial and naloxone, 1.2 mg, on the other trial. Vertical bars represent SEM.

induced by high intensity, acupuncture-like stimulation.

Although there is controversy concerning the dose of naloxone needed to reverse the effects of endogenous opiates, there is evidence that naxolone, 0.4 mg, given intravenously should reverse the analgesia of a treatment that relieves pain by release of endorphins or enkephalins. Adams (6) reported partial reversal of analgesia produced by central gray stimulation in man with as little as naloxone, 0.05 mg, and marked reversal by 0.25 mg IV. Chapman and Benedetti (1) were able to antagonize the analgesic effect of high intensity, low frequency peripheral stimulation with naloxone, 0.4 mg. The results we obtained in five patients using naxolone, 1.2 mg, confirms the lack of reversal of analgesia in the 10 patients receiving the lower dose.

The literature indicates that peripheral electrical stimulation that produces analgesia associated with endorphine release (7) or reversible by naloxone (1,5,8) must be of high intensity (at or above pain thresholds) and low frequency. It is not clear whether

frequency or intensity is the critical factor in activating endogenous opiate mechanisms. Analgesic effects of low frequency, low intensity stimulation have not been reported, and high frequency stimulation at high currents are not tolerated because of tetanic muscle contraction. It might be postulated that stimuli that exceed the pain threshold activate opiate-mediated pain control mechanisms. Mechanical acupuncture, acupressure, and manipulation therapy, all of which are described by patients as painful, might act through such a mechanism; however, there is no literature to support such an hypothesis.

There is evidence that nonpainful treatments for pain (excluding administration of narcotics) are not reversed by naloxone. Goldstein and Hilgard (9) have reported the failure of naloxone to modify hypnoanalgesia. D. Mihic (personal communication) has demonstrated that naloxone, 0.4 mg, does not antagonize placebo analgesia. Levine et al (10) were partially able to reverse placebo analgesia with naloxone, but only with very large doses (10 mg) which, as Hayes et al (11) suggest, may produce pharmacologic effects other than inactivation of opiate-mediated pain-controlling pathways.

This study adds further evidence that endorphin- or enkephalin-mediated pathways are not activated by conventional low intensity, high frequency transcutaneous electrical stimulation in patients with chronic pain. The mechanism of action of this method of treatment of pain in such patients remains a question. A placebo effect has been demonstrated for transcutaneous stimulation (12). Since placebo analgesia tends to diminish with time (13), we felt we could eliminate many placebo responders by using patients who had successfully used a stimulator for at least 1 month. A dorsal horn "gating" mechanism (14) is another possible explanation. Alterations in peripheral nerve transmission may also be involved. Torrebjörk and Hallin (15) have demonstrated increased latency and blocking in peripheral nerves, more pronounced in C fibers than in A fibers, during intradermal electrical stimulation. Alterations in sympathetic tone may also play a role in the production of analgesia (16).

REFERENCES

1. Chapman RN, Benedetti C. Analgesia following transcutaneous electrical stimulation and its partial reversal by a narcotic antagonist. Life Sci 1977;21:1645–8.
2. Sjölund B, Eriksson M. Electro-acupuncture and endogenous morphines. Lancet 1976;2:1085.
3. Mayer DJ, Price DD, Rafii A. Antagonism of acupuncture analgesia in man by the narcotic antagonist naloxone. Brain Res 1977;121:368–72.
4. Woolf CJ, Mitchell D, Meyers RA, Barrett GD. Failure of naloxone to reverse peripheral transcutaneous electro-analgesia in patients suffering from acute trauma. S Afr Med J 1978;53: 179–80.
5. Sjölund BH, Eriksson MBE. The influence of naloxone on analgesia produced by peripheral conditioning stimulation. Brain Res 1979;173:295–301.
6. Adams JE. Naloxone reversal of analgesia produced by brain stimulation in the human. Pain 1976;2:161–6.
7. Sjölund B, Terenius L, Eriksson M. Increased cerebrospinal fluid levels of endorphins after electroacupuncture. Acta Physiol Scand 1977;100:382–4.
8. Cheng RSS, Pomeranz B. Electroacupuncture analgesia could be mediated by at least two pain-relieving mechanisms: endorphin and non-endorphin systems. Life Sci 1979;25:1957–62.
9. Goldstein A, Hilgard DR. Failure of opiate antagonist naloxone to modify hypnotic analgesia. Proc Natl Acad Sci USA 1975;72: 2041–3.
10. Levine JD, Gordon NC, Fields HL. The mechanism of placebo analgesia. Lancet 1978;2:654–7.
11. Hayes R, Price DD, Dubner R. Naloxone antagonism as evidence for narcotic mechanisms. Science 1977;196:600.
12. Thorsteinsson G, Stonnington HH, Stillwell GK, Elveback LR. The placebo effect of transcutaneous electrical stimulation. Pain 1978;5:31–41.
13. Evans FJ. The placebo response in pain reduction. In: Bonica JJ, ed. Advances in neurology. New York: Raven Press, vol 4, 1974.
14. Melzack R, Wall PD. Pain mechanisms: a new theory. Science 1965 0:971–9.
15. Torrebjörk EH, Hallin RG. Responses in human A and C fibers to repeated electrical intradermal stimulation. J Neurol Neurosurg Psychiatry 1974;37:653–64.
16. Abram SE, Asiddao CB, Reynolds AC. Increased skin temperature during transcutaneous electrical stimulation. Anesth Analg 1980;50:22–5.

ANESTH ANALG
60:85-90, 1981

Atropine and Glycopyrrolate Effects on Lung Mechanics in Normal Man

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GAL, T. J., AND SURATT, P. M.: Atropine and glycopyrrolate effects on lung mechanics in normal man. Anesth Analg 1981;60:85-90.

To assess the comparative bronchomotor effects of large systemic doses of glycopyrrolate and atropine intravenous glycopyrrolate (10 μg/kg), atropine (20 μg/kg), or a placebo was administered to six healthy male volunteers in double-blind fashion. Both drugs produced bronchodilation reflected by significant decreases in airway resistance and increases in specific airway conductance (sGAW) compared to placebo. Glycopyrrolate increased sGAW to a maximal level of 100% ± 7% above control; bronchodilation persisted at this level for more than 4 hours after drug administration. Atropine increased sGAW to a maximum of 88% ± 5% above control 30 minutes after administration, but sGAW returned to control levels between 3 and 4 hours after the drug was given. Both drugs increased maximum expiratory flow rates over the same time course as sGAW, but the percent increases in flow were significantly less than changes in sGAW. Lung elastic recoil was decreased by both drugs over the full range of lung volume. The 32% maximum increase in heart rate after glycopyrrolate was significantly less ($p < 0.01$) than the 60% increase after atropine. It was concluded that vagal blockade with glycopyrrolate dilates large and small airways to the same extent as atropine, but that the effect is more sustained and associated with less cardiac vagal blockade. Lower doses of glycopyrrolate were also studied and the findings showed that maximal bronchodilation is achieved with lower doses (3.2 μg/kg), which are commonly used in routine premedication.

Key Words: AIRWAY: resistance; LUNG: compliance, function; PARASYMPATHETIC nervous system: glycopyrrolate, atropine; PREMEDICATION: anticholinergic, glycopyrrolate, atropine.

ATROPINE, the classic anticholinergic drug, has recognized bronchodilating actions that lower airway resistance (1) and increase dead space (2). The bronchodilation is clinically significant, however, only when large systemic doses (>1.2 mg) are administered. Such doses effectively block reflex bronchoconstriction due to airway irritation (3, 4), but produce undesirable side effects including tachycardia and central nervous system symptoms (5). These adverse effects, in addition to the relatively short-lived effects of atropine on airways (6), have limited the drug's clinical usefulness as a bronchodilator.

Glycopyrrolate, a quaternary ammonium compound with a similar spectrum of activity, was originally introduced as an anticholinergic drug to control gastric acidity (7). Recently the drug has enjoyed widespread use as an adjunct to anesthetic practice. Its potency is about twice that of parenteral atropine both as an antisialagogue (8) and as an antimuscarinic during reversal of neuromuscular blockade (9). Glycopyrrolate may possess bronchodilating properties, but its bronchomotor effects have not been examined. The purpose of this study was to compare the bronchodilating actions of glycopyrrolate to atropine, noting their peak response, duration of action, and side effects when given systemically in doses likely to produce significant vagal blockade. In addition, to determine the dose-response characteristics of glycopyrrolate, airway function was measured after four decreased doses of the drug.

Methods

Six healthy men, 21 to 34 years of age, with normal pulmonary function participated in the study. All were nonsmokers with no history or symptoms of respiratory disease. They gave informed consent after approval of the protocol by the Human Studies Com-

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Received from the Department of Anesthesiology and the Pulmonary Division, Department of Internal Medicine, University of Virginia Medical Center, Charlottesville, Virginia 22908. Accepted for publication November 3, 1980. Presented in part at the Annual Meeting of the American Society of Anesthesiologists, St. Louis, Missouri, October 1980.
Reprint requests to Dr. Gal.

mittee of the University of Virginia. Using a double-blind, randomized crossover technique we administered intravenous injections of either glycopyrrolate (10 μg/kg), atropine (20 μg/kg), or placebo to subjects on separate days. The atropine dose was chosen to achieve significant vagal blockade of the airways (4, 5). The glycopyrrolate dose was based on its 2-fold potency compared to atropine (8, 9).

Pulmonary function studies were performed with subjects in the seated position before each treatment (control) and were repeated ½, 1, 2, 3, and 4 hours after treatment. We also recorded pulse rates and the subjects' subjective symptoms at these times. In addition, airway resistance and flow-volume curves were measured 7 hours after each treatment in four of the six subjects.

Airway resistance (RAW) and functional residual capacity (FRC) were measured by the method of DuBois and co-workers (10, 11) using a variable pressure constant volume body plethysmograph. RAW measured at FRC was converted to its reciprocal airway conductance (GAW). To eliminate changes produced by variations in lung volume, GAW was expressed as specific conductance (sGAW) by dividing GAW by FRC (12). The mean values from 10 satisfactory measurements were used in the results.

Forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) were measured with a model 840 waterless rolling seal spirometer (Ohio Medical Products, Madison, WI). All volumes were corrected to body temperature and pressure saturated with water vapor. The best effort defined by the curve with the largest FVC and FEV_1 was used for analysis. During the forced expiration flow derived by electronic differentiation of the spirometer's volume signal was also plotted against volume on a fast response X-Y recorder (model 7041A, Hewlett-Packard Co, Waltham, MA) to obtain maximum expiratory flow volume (MEFV) curves from which peak expiratory flow (PEFR) and expiratory flow at midvital capacity ($\dot{V}$max 50) were quantitated. To obtain a partial expiratory flow-volume (PEFV) curve, subjects, after a quiet exhalation to FRC, inspired to about 60% of vital capacity and then forcefully exhaled to residual volume (RV) and expiratory flow vs lung volume was recorded. Immediately after recording the PEFV curve, subjects inspired maximally to total lung capacity (TLC) and then expired forcefully to RV to obtain a reference MEFV curve. Flow was quantitated at 40% of FVC above RV ($\dot{V}$max 40) or more specifically at TLC minus 60% of FVC (13). Curves were only used in the results if RV for PEFV and reference MEFV curve coincided.

Lung elastic recoil was measured from expiratory pressure volume curves by a quasistatic method. Transpulmonary pressure was estimated as the difference between the pressure at the mouth and esophageal pressure (13). A 10-cm long balloon containing 0.5 ml of air was placed in the midesophagus and connected to a Validyne MP-45 differential pressure transducer (range ± 50 cm H_2O) (Validyne Engineering Corp, Northridge, CA); the opposite side of the transducer was connected to a pressure tap in the mouthpiece. Transpulmonary pressure was simultaneously plotted against lung volume on the X-Y recorder while subjects inspired to TLC and then expired slowly (approximately 0.2 L/sec) to RV. A line of best fit was drawn by eye through at least three sets of pressure volume data that agreed ± 1 cm H_2O. The static recoil pressure of the lung (PSTL) was estimated from transpulmonary pressure measured at 10% intervals of TLC calculated by adding the mean inspiratory capacity to FRC during the recording of pressure volume curves.

Finally, the dose-response characteristics of glycopyrrolate were assessed by administering four decreased doses of the drug (1 μg/kg, 1.9 μg/kg, 3.2 μg/kg, and 6.1 μg/kg) in random sequence to each of the six subjects on separate days. In this experiment measurements of RAW and FRC were made 2 hours after drug administration.

Statistical significance of the changes after each drug compared to placebo was analyzed with the paired *t*-test; $p < 0.05$ was considered statistically significant. Values are expressed as means ± SEM.

Results

Mean RAW decreased and sGAW increased significantly after both atropine and glycopyrrolate (Fig 1, A and B). Inasmuch as FRC did not change significantly with either drug ($p > 0.05$), the changes in RAW and sGAW appeared to be mirror images of each other. The maximum increase in sGAW with glycopyrrolate (100% ± 7% above control) occurred 2 hours after the drug was administered and remained at this level for more than 4 hours. Seven hours after administration of glycopyrrolate sGAW in four subjects was still 56% above control levels. The peak increase in sGAW with atropine (88% ± 5% above control) did not differ significantly from that with glycopyrrolate ($p < 0.01$, paired *t*-test). In contrast to glycopyrrolate,

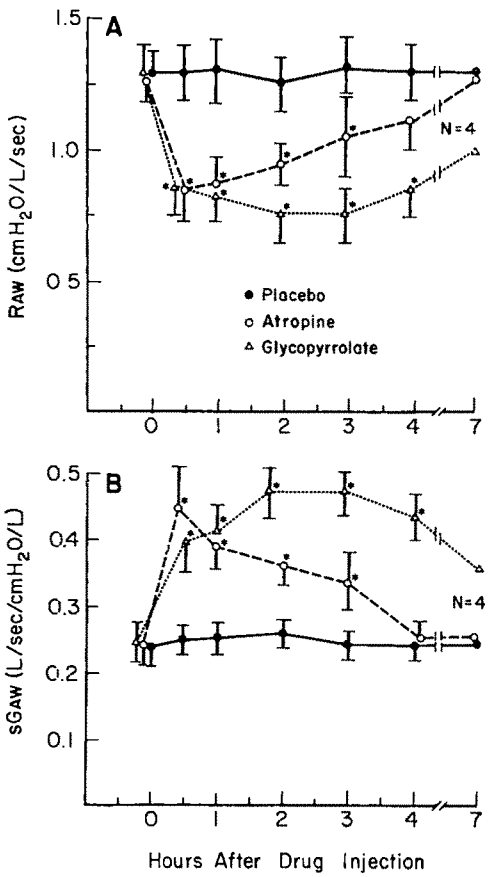


FIG 1. Time-related changes in airway resistance (RAW) after drug administration (A) and changes in specific airway conductance (sGAW) (B). Values are means ± SEM for six subjects; * $p < 0.01$ denotes significant difference from placebo (paired *t*-test).

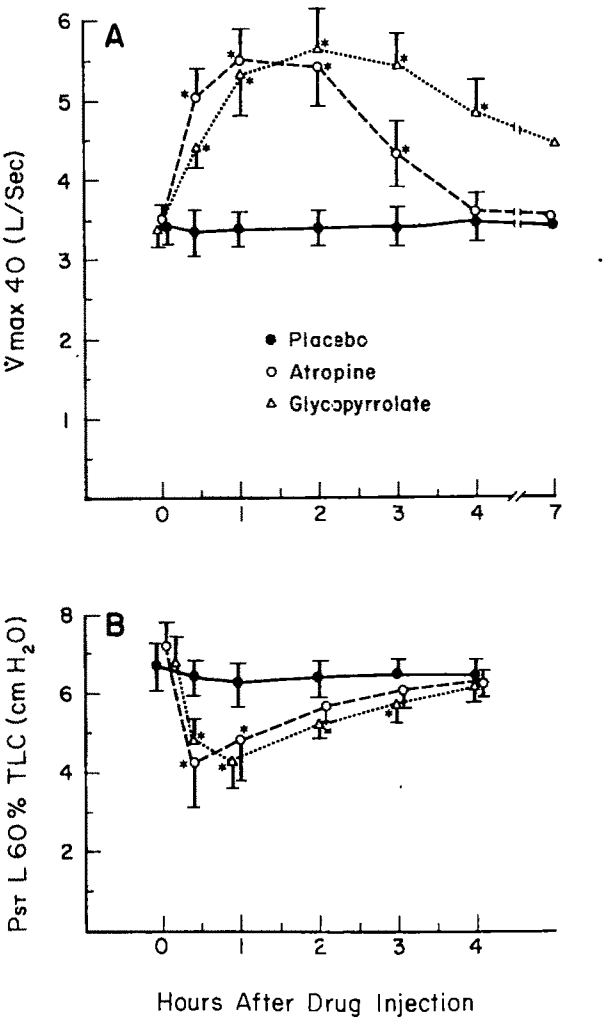


FIG 2. Time-related changes in V̇max 40 (A) and changes in lung elastic recoil pressure (PSTL) at 60% of total lung capacity (TLC) (B). Values are mean ± SEM for six subjects. V̇max 40 = expiratory flow at TLC—60% of forced vital capacity (FVC), i.e., 40% of FVC above residual volume; * $p < 0.01$ denotes significant difference from placebo (paired *t*-test).

sGAW after atropine reached its maximum 30 minutes after the drug and declined progressively, reaching control levels between 3 and 4 hours after the drug.

Maximum increases in V̇max 40 after glycopyrrolate and atropine were 72% and 60% above control levels, respectively; these statistically significant time-related changes paralleled those of sGAW (Fig 2, A). PSTL decreased after both glycopyrrolate and atropine. The changes were significantly different from placebo ($p < 0.01$) at all lung volumes 1 hour after the drugs were given (Fig 3). The time-related changes in PSTL at 60% of TLC (a lung volume near normal inspiration) indicate that the maximal decrease in PSTL occurred at this time interval (Fig 2, B).

Maximum expiratory flow rates were related to PSTL at the same lung volumes to plot maximum flow-static recoil curves (Fig 4). At any level of PSTL the expiratory flow rates were increased significantly after atropine and glycopyrrolate compared to placebo ($p < 0.01$).

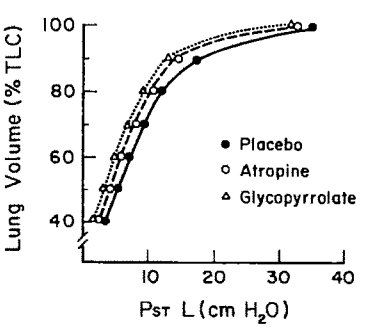


FIG 3. PSTL plotted vs lung volume expressed as percent of TLC 1 hour after drug administration. Values of PSTL are means for six subjects after placebo, atropine, or glycopyrrolate.

FVC did not change significantly, but other parameters such as FEV_1, PEFR, and $\dot{V}max$ 50 increased significantly above control ($p < 0.01$) after both drugs and their time course paralleled changes in sGAW. However, the maximal changes PEFR (11% above control), FEV_1 (3%), and $\dot{V}max$ 50 (19%) were considerably less than changes in sGAW.

Heart rate reached its maximum (32% above control) ½ hour after glycopyrrolate (Fig 5). This increase was significantly less ($p < 0.01$) than the 60% increase following atropine. Subjective sensations of dry mouth were more severe and persistent after glycopyrrolate than after atropine. Subjects noted dryness of the mouth up to 10 hours following glycopyrrolate. None of the subjects receiving glycopyrrolate experienced visual blurring, drowsiness, or lightheadedness described by four of the six subjects after atropine.

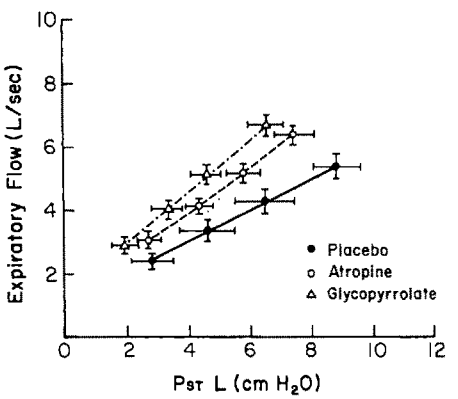


FIG 4. Mean maximum flow-static recoil curves in six subjects 1 hour after placebo, atropine, or glycopyrrolate. Expiratory flows at 10% intervals of TLC between 70% and 40% TLC are plotted against PSTL. Bars indicate means ± SEM for both flow and pressure.

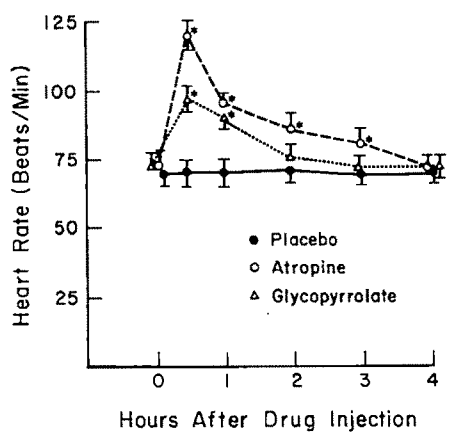


FIG 5. Time-related changes in heart rate following drug administration. Values are means ± SEM for six subjects. * $p <$ 0.01 denotes significant difference from placebo (paired t-test).

Maximal increases in sGAW occurred after glycopyrrolate doses of approximately 3.2 mg/kg (Fig 6). These are considerably lower than doses used in the first portion of the study and are similar to those used in routine preanesthetic medication.

Discussion

This study demonstrates that glycopyrrolate administered intravenously is an effective bronchodilating drug in normal subjects. Effects on the airways are qualitatively and quantitatively similar to atropine in large doses, but are associated with less cardiac vagal blockade. Dose-response data (Fig 5) suggest that similar maximal bronchodilation (sGAW 100% above control) occurs with smaller doses of glycopyrrolate (3.2 μg/kg). Such doses are commonly used as preanesthetic medication and are associated with minimal changes in heart rate. In contrast, premedicant doses of atropine (6 to 8 μg/kg) increase sGAW less than 50% above control while significantly increasing heart rate (6, 14).

The measurement of sGAW in normal subjects reflects, for the most part, the dimensions of the larynx and the larger central airways (trachea and major bronchi) (15). The increases in sGAW observed after both drugs imply that a marked increase occurs in the caliber of these airways. Despite this bronchodilation, maximum increases in FEV_1, PEFR, and $\dot{V}max$ 50 were less dramatic. This apparent dichotomy between increases in sGAW and expiratory flow rates has been noted previously (1). After smooth muscle relaxation,

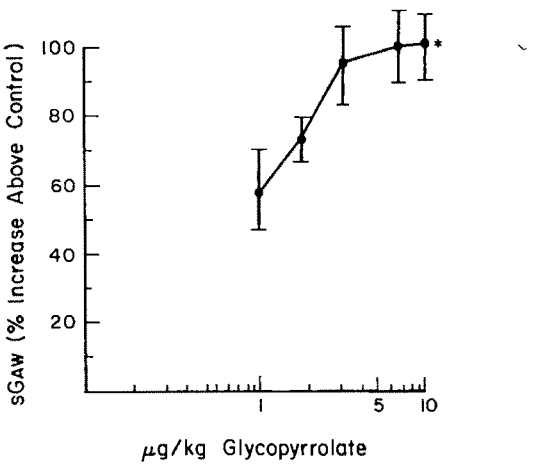


FIG 6. Dose-response curve for bronchodilation after glycopyrrolate. Percent increase in sGAW is plotted as a function of increasing dose on a log scale. Values are means ± SEM for six subjects. * Denotes large systemic dose (10 μg/kg) used in initial phase of study to produce significant vagal blockade in airways.

the large airways become more compressible in the presence of the high transmural pressures associated with forced expiration; this tends to limit increases in expiratory flows (16). During the low flow rates at which sGAW is measured, transmural stress on the airways is small and relaxation of bronchial smooth muscle is more directly reflected by increases in sGAW.

Compared to sGAW, the measurements of flow during maximal forced expiratory maneuvers reflect more the properties of the lung and more distal airways (17). Flow measurements during PEFV curves are particularly sensitive to changes in airway tone and possess the distinct advantage of being unaffected by upper airway resistance (18). Both atropine and glycopyrrolate increased flow rates on PEFV curves ($\dot{V}$max 40). These changes suggest dilation of peripheral airways; however, a fuller explanation of the changes in expiratory flows requires a consideration of the other force responsible for flow, PSTL. According to the theory of Mead et al (19), expiratory flow may be increased by a decrease in small airway resistance, but also by an increased PSTL. PSTL decreased after both atropine and glycopyrrolate. The increased flow in face of the decreased PSTL (Fig 4) must result from a decreased resistance or, more specifically, a dilation of smaller peripheral airways.

The decreased PSTL observed after glycopyrrolate treatment could represent an artifact due to an increase in esophageal tone as a result of the drug. However, esophageal tone was decreased by glycopyrrolate in this study and by atropine in a previous study (20). This would tend to minimize decreases in PSTL and thus could not explain the observed decrease in PSTL. The most likely cause for the decreased lung recoil is dilation of peripheral lung units including the alveolar ducts. This may increase alveolar size and in turn reduce lung retractile pressure. Such a loss of lung elastic recoil might be expected to produce an increase in FRC since the latter volume reflects the balance between the outward recoil of the chest wall and the inward recoil of the lung. In this study neither glycopyrrolate nor atropine produced consistent increases in FRC compared to placebo. These results are at variance with the findings of DeTroyer et al (20) who recently noted a consistent increase in FRC shortly after vagal blockade with atropine. The mean increase they noted was small (250 ml) and was similar in magnitude to the variations of FRC in our subjects following treatment with placebo.

The sensitivity of various end organs to effects of anticholinergic drugs differs considerably. However, the magnitude and duration of the bronchodilating action of glycopyrrolate parallels its activity as an antisialagogue (21). This sustained, profound drying effect renders the use of parenteral glycopyrrolate impractical as a bronchodilator in ambulatory patients. On the other hand, its prolonged effects on the airways may prove useful in patients with bronchial hyperreactivity who must undergo general anesthesia. In these patients a reduction in the resting bronchomotor tone is likely to decrease the bronchoconstrictive response to irritant stimuli such as tracheal intubation (22).

Until recently the clinical use of anticholinergics has been restricted because of concerns that they cause slowing of mucus transport by increasing viscosity of secretions. This in turn could cause mucus inspissation and thus increase airway obstruction. Conflicting reports, however, indicate that intravenous atropine inhibits (23), or increases (24) mucociliary transport. Short- and long-term observations in patients with airway hypersecretion strongly suggest that anticholinergic agents can effectively and safely relieve airway obstruction and aid expectoration (25).

We conclude that in normal subjects intravenous glycopyrrolate produces dilation of large central airways that is reflected by increases in sGAW. Increases in $\dot{V}$max 40 and decreased PSTL suggest that dilation of peripheral airway units occurs as well. This bronchodilation is similar qualitatively and quantitatively to that with large systemic doses of atropine, but is associated with less cardiac vagal blockade and no central nervous system effects. The airway effects of glycopyrrolate are sustained near maximal values following a single intravenous dose in contrast to the relatively short-lived effects of atropine. In addition, maximal bronchodilation is achieved with common premedicant doses of glycopyrrolate, well below those producing significant vagal blockade. Glycopyrrolate thus appears to be a potentially valuable adjunct to anesthesia for patients in whom reflex airway reactivity is likely, particularly for those with concomitant cardiac disease.

ACKNOWLEDGMENTS

The authors wish to thank Ms. Donna Hooe for her invaluable technical assistance. Drug preparations and stipends for volunteer subjects were provided by A. H. Robins Co, Richmond, VA.

REFERENCES

1. Butler J, Caro CG, Alcala R, Dubois AB. Physiologic factors affecting airway resistance in normal subjects and in patients with obstructive respiratory disease. J Clin Invest 1960;39:584–91.

2. Severinghaus JW, Stupfel M. Respiratory dead space increase following atropine in man, and atropine, vagal, or ganglionic blockade and hypothermia in dogs. J Appl Physiol 1955;8:81–7.
3. Widdicombe JG, Kent DC, Nadel JA. Mechanism of bronchoconstriction during inhalation of dust. J Appl Physiol 1962;17: 613–6.
4. Simonsson BG, Jacobs FM, Nadel JA. Role of the autonomic nervous system and the cough reflex in the increased responsiveness of airways in patients with obstructive airway disease. J Clin Invest 1967;46:1816–7.
5. Yu DYC, Galant SP, Gold WM. Inhibition of antigen induced bronchoconstriction by atropine in asthmatic patients. J Appl Physiol 1972;32:823–8.
6. Smith TC, DuBois AB. Effects of scopolamine on the airways of man. Anesthesiology 1969;30:12–8.
7. Sun DCH. Comparative study of the effect of glycopyrrolate and propantheline on basal gastric secretion. Ann NY Acad Sci 1962;99:153–7.
8. Wyant GM, Kao E. Glycopyrrolate methylbromide: effect on salivary secretion. Can Anaesth Soc J 1972;21:230–41.
9. Rammamurthy S, Shaker MH, Winnie AP. Glycopyrrolate as a substitute for atropine in neostigmine reversal of muscle relaxant drugs. Can Anaesth Soc J 1972;19:399–411.
10. DuBois AB, Botheho SY, Comroe JH. A new method for measuring airway resistance in man using a body plethysmograph: values in normal subjects and in patients with respiratory disease. J Clin Invest 1957;35:327–34.
11. DuBois AB, Botheho SY, Bedell GN, Marshall R, Comroe JH. A rapid plethysmographic method for measuring thoracic gas volume: a comparison with a nitrogen washout method for measuring functional residual capacity in normal subjects. J Clin Invest 1956;35:322–6.
12. Briscoe WA, DuBois AB. The relationship between airway resistance, airway conductance, and lung volume in subjects of different age and body size. J Clin Invest 1958;37:1279–85.
13. Bouhys A. The physiology of breathing. New York: Grune and Stratton, 1977:215.
14. Kjellberg M, Heinonen J. Atropine, neostigmine and airway resistance. Acta Anaesthesiol Scand 1974;18:209–14.
15. Hogg JC, Macklem PT, Thurlbeck WM. Site and nature of airway obstruction in chronic obstructive lung disease. N Engl J Med 1968;278:1355–60.
16. Bouhys A, Van De Woestijne KP. Mechanical consequences of airway smooth muscle relaxation. J Appl Physiol 1971;30:670–6.
17. Ingram RH, McFadden ER. Localization and mechanism of airway responses. N Engl J Med 1977;297:596–600.
18. Bouhys A, Hunt VR, Kim MB, Zapletal A. Maximum expiratory flow rates in induced bronchoconstriction in man. J Clin Invest 1969;48:1159–68.
19. Mead J, Turner JM, Macklem PT, Little JB. Significance of the relationship between lung recoil and maximum expiratory flow. J Appl Physiol 1967;22:95–108.
20. DeTroyer A, Yernault JC, Rodenstein D. Effects of vagal blockade on lung mechanics in normal man. J Appl Physiol 1979;46: 217–26.
21. Mirakhur RK, Dundee JW, Jones CJ. Evaluation of the anticholinergic actions of glycopyrronium bromide. Br J Clin Pharmacol 1978;5:77–84.
22. Benson MK. Bronchial hyperreactivity. Br J Dis Chest 1975;69: 227–239.
23. Annis P, Landa J, Lichtiger M. Effects of atropine on velocity of tracheal mucus in anesthetized patients. Anesthesiology 1976;44:74–7.
24. Chopra SK. Effect of atropine on mucociliary transport velocity in anesthetized dog. Am Rev Respir Dis 1978;118:367–71.
25. Gold WM. The role of the parasympathetic nervous system in airway disease. Postgrad Med J 1975;51(Suppl 7):53–62.

Intracardiac Injections during Cardiopulmonary Resuscitation

Fifty-three patients were observed prospectively for the development of complications resulting from 147 intracardiac injections received during cardiopulmonary resuscitation (CPR). Patients in an intensive care unit were included in the study if they had received intracardiac injections and met one of the following conditions: successful CPR with survival for more than 24 hours; successful CPR with survival for less than 24 hours and a full autopsy secured; CPR not successful and a full autopsy secured. Although pericardial effusion was noted in six of 17 echocardiograms and a hemopericardium was found in eight of 28 autopsies, cardiac tamponade was not observed. A pneumothorax developed in one patient. None of the autopsies disclosed coronary artery or ventricular lacerations. Percutaneous puncture of the heart during CPR seldom results in serious complications. When other sites are not readily available, intracardiac injections are safe and appropriate for the administration of emergency medication. *(Davison R, Barresi V, Parker M, Meyers SN, Talano JV: Intracardiac injections during cardiopulmonary resuscitation: a low risk procedure. JAMA 1980; 244:1110–1).*

SPECIAL
article

Cyclic Nucleotides in Neuromuscular Transmission

Frank G. Standaert, MD,* and Kenneth L. Dretchen, PhD†

MOTOR NERVE terminals perform the first step in neuromuscular transmission, the conversion of an electrical signal in the nerve membrane to a chemical impulse that can cross the junctional cleft. The electrical sequences in nerves are familiar and quite well understood, and so are the steps in the synthesis of acetylcholine. But, these are the skeleton; still missing is an understanding of the dynamic processes that connect the electrical and chemical sequences and make the system vital. The connecting processes, usually grouped under the term excitation-secretion coupling, are the object of research and speculation which are considering the roles of cyclic adenosine monophosphate (cAMP), calcium, sodium, and prejunctional receptors in motor nerve endings. The results are providing new insights into neuromuscular function and the ways in which drugs affect neuromuscular transmission.

cAMP has been implicated in many actions in many cells. In most of these it acts as a "messenger" between receptors in the cell membrane and operational components inside the cell. The essential steps of cyclic nucleotide biochemistry are illustrated in Fig 1; the details may be found in many reviews (1, 2). Adenylate cyclase, an enzyme in the cell membrane which requires activation by a triggering process, such as the reaction of a receptor with its specific agonist, converts adenosine triphosphate (ATP) to cAMP. cAMP activates one or more of a second group of enzymes, protein kinases, which transfers a phosphate from ATP to operational proteins. These phosphorylated proteins regulate cellular functions including: cell secretion, ion flux, metabolism, and protein synthesis. A third group of enzymes, cAMP phosphodiesterases, inactivates cAMP by hydrolyzing it to 5'-adenosine monophosphate (5'-AMP).

There is substantial evidence that cAMP is part of the excitation-secretion system of motor nerve endings. The most basic is the capacity of compounds that should increase the activity of cAMP in nerve endings to increase the flow of ions into and the release of transmitter from the ending. cAMP itself is not useful for experiments with intact cells because it is so poorly soluble in lipid that it does not adequately penetrate the cell membrane; therefore, lipid-soluble derivatives, such as dibutyryl cAMP, (dbcAMP) or compounds that inhibit phosphodiesterase, such as theophylline, commonly are used to increase intracellular cAMP.

The effects of dbcAMP on cat soleus motor nerve endings are shown in Fig 2. The traces are records of activity in single axons from animals anesthetized with alpha-chloralose. Stimulation was applied to the peripheral nerve, and antidromically propagated action potentials were recorded from the root of the motor axon. Drugs were injected rapidly into the artery of the soleus muscle (for method see reference 3). The trace in Fig 2, a is a record made with the oscilloscope beam moving very slowly. The axon was stimulated once every 2.5 seconds and the potentials marked S were evoked by those stimuli. dbcAMP was

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Supported in part by United States Public Health Service Grant #NS, 12,566 and by National Science Foundation Grant #BNS-78-26849.

Received from the Department of Pharmacology, Georgetown University, Schools of Medicine and Dentistry, Washington, DC. Accepted for publication October 24, 1980. Portions of this material were presented at the Postgraduate Assembly of the New York State Society of Anesthesiologists, December 1979.

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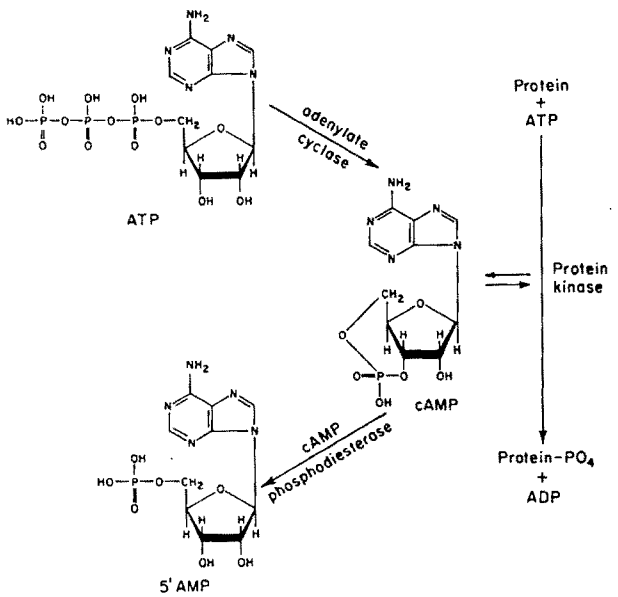


FIG 1. Reactions in formation and hydrolysis of cAMP.

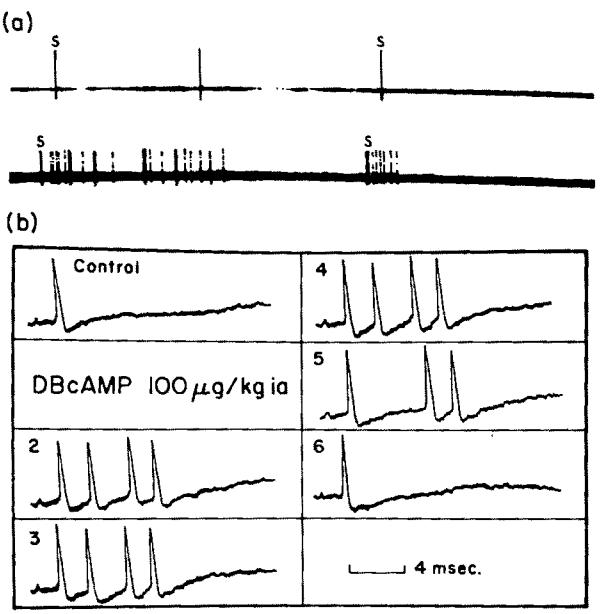


FIG 2. Effects of dbcAMP on motor axons from cat soleus nerve. a, Potentials marked S were evoked by stimuli applied once every 2.5 seconds. Other potentials were initiated by intra-arterial injection of dbcAMP, 100 μg/kg. Each trace is a separate experiment. b, Traces showing action potentials evoked by a single stimulus applied every 2.5 seconds: first trace before injection of dbcAMP, others at successive 2.5-second intervals after intra-arterial injection of dbcAMP (100 μg/kg). (Reproduced with permission from Standaert et al (5)).

injected between the stimuli, and all the action potentials except those marked S were initiated by that injection. This burst of action potentials, drug-initiated activity (DIA), is a signal that dbcAMP depolarized the nerve ending and indicates that the nucleotide caused enough ionic flux across the nerve membrane to initiate action potentials.

dbcAMP also causes a change in the nerve's response to stimulation. The records in Fig 2, b were made with the oscilloscope beam set to record nerve potentials evoked by single stimuli. The first trace, made before the injection of dbcAMP, shows the usual response of an axon; the single stimulus evokes a single action potential. Subsequent traces show the effect of the nucleotide; in its presence the nerve fires repetitively. This stimulus-bound repetitive activity (SBR) is another signal that dbcAMP increased ion flux in the nerve ending, in this case prolonging the negative afterpotentials (4).

This neural activity is transmitted to the muscle (Fig 3). The neural DIA causes a burst of fasciculations and contractions in unstimulated muscles (Fig 3, a) or between the stimulus-evoked contractions in stimulated preparations (Fig 3, b and c). The neural SBR provides a train of repetitive stimuli to the muscle and evokes a brief tetanic contraction which is much stronger than the simple twitch evoked by the single action potential of the control period (Fig 3, b and c). dbcAMP has no effect on denervated muscle (Fig 3, d).

DIA and SBR are produced by monobutyryl or dibutyryl cAMP but not by cAMP, cyclic guanosine monophosphate (cGMP), 5'-AMP or butyrate (5). These observations led us to conclude that derivatives of cAMP that can penetrate the cell membrane act inside the cell to cause a flow of depolarizing ions into the nerve ending. We are quite certain that the

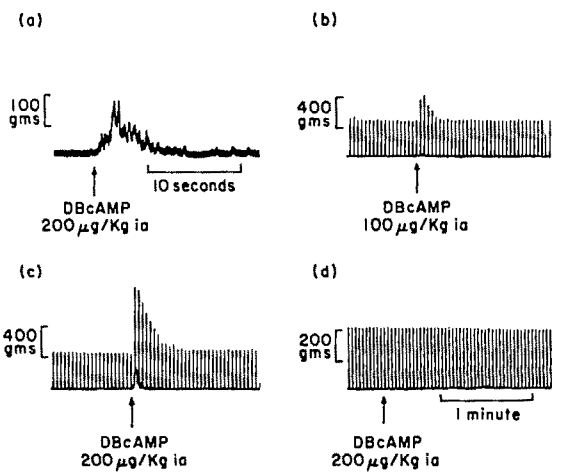


FIG 3. Effects on contraction of soleus muscle produced by dbcAMP injected intra-arterially. a, Nerve not stimulated, contractions evoked by dbcAMP; b and c, Nerve stimulated supramaximally every 2.5 seconds: d, denervated muscle stimulated directly. (Reproduced with permission from Standaert et al (5)).

DIA and SBR are neurogenic because neither cAMP nor its lipid soluble derivatives has any action on motor endplates or muscle that might cause retrograde depolarization of the nerve ending; these cyclic nucleotides have no effect on denervated muscle and none of the investigators who applied them directly on endplates noticed depolarization (6–9). On the other hand, microinjection of dbcAMP into the cell body of a motoneuron causes depolarization and prolongation of afterpotentials (10).

The question of whether cAMP is endogenous and has a physiologic function in nerve endings is more difficult to answer because the nerve endings are so small that they have not yet been subjected to direct chemical analysis. Even so, there is ample evidence to support the thesis that cAMP has a function in motor nerve endings. For example, if cAMP were endogenous in nerve endings, drugs that inhibit phosphodiesterase would cause accumulation of the nucleotide and thereby mimic the effects of exogenous material. Fig 4a illustrates the effects of theophylline on muscle contraction. There are fewer fasciculations in proportion to the potentiation of force of stimulated muscle, but otherwise the effects are similar to those of dbcAMP. Although not illustrated here, we have shown that the changes in muscle contraction are due to drug-induced SBR and DIA in motor nerve endings (11). Theophylline and other phosphodiesterase inhibitors produce similar potentiation of contraction force in isolated rat diaphragms (12–14).

We also tested the capacity of theophylline to increase the activity of dbcAMP. As shown in Fig 4b, a dose of theophylline too small to produce an overt effect greatly increased the response to the nucleotide.

Most laboratories doing similar experiments use theophylline with the assumption that observed effects are due to inhibition of phosphodiesterases, even though theophylline has other actions. To deal with the possibility that one of the other actions might be responsible for the DIA or SBR we experimented with a variety of other compounds including isopropylbutylmethylxanthine (IBMX), papaverine, and SQ 20,009, which share theophylline's capacity to inhibit phosphodiesterase but not its other characteristics. All acted like theophylline on soleus nerve endings (15).

If cAMP is a normal, functional constituent of motor nerve endings, then the enzymes that make and destroy it and through which it acts, must be present in the endings. The endings have not been directly assayed, but Breckenridge and Bray (16) found phosphodiesterase activity in chicken sciatic

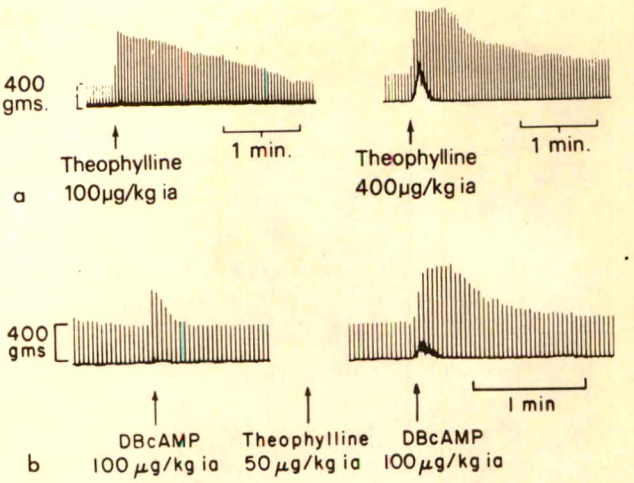


FIG 4. Effects of theophylline on cat soleus muscle stimulated supramaximally every 2.5 seconds: a, theophylline, 100 µg and 400 µg/kg: b, records of two injections of dbcAMP 5 minutes apart; theophylline, 50 µg/kg was administered 1 minute before the second injection. All injections were made intra-arterially.

nerve and Horn and McAfee (17) found cAMP, cGMP, and the corresponding nucleotidyl cyclases and phosphodiesterases in frog sciatic nerves. Both teams showed that the enzymes accumulated rostral to a ligature around the nerve, a sign that they were being moved from the cell body toward the nerve endings by rapid axonal transport. We confirmed these observations by determining phosphodiesterase in cat sciatic nerves. The enzyme is present in both soluble and particulate fractions of a homogenate and each fraction contains a high and a low affinity form of enzyme. All four forms accumulate rostral to a ligature (18).

We also conducted a pharmacologic analysis in which a number of chemicals known to activate or inhibit one or another part of the system sketched in Fig 1 were administered alone or sequentially. The results are compatible with the hypothesis that a system for forming and degrading cAMP is present in soleus nerve endings and that it has a functional role in neuromuscular transmission (11, 15).

Additional evidence, perhaps the most direct yet, obtained for the presence of cAMP in motor nerve endings, is presented in Fig 5. It contains two sequential sections 5 µ apart through a rat soleus neuromuscular junction. The section on the left was treated to reveal acetylcholinesterase and reproduces the familiar pattern of this enzyme at the neuromuscular junction. The section on the right was treated with an antibody to cAMP that had been coupled to a fluorescent dye. The illuminated spots correspond to the location of cAMP and clearly show cAMP at the

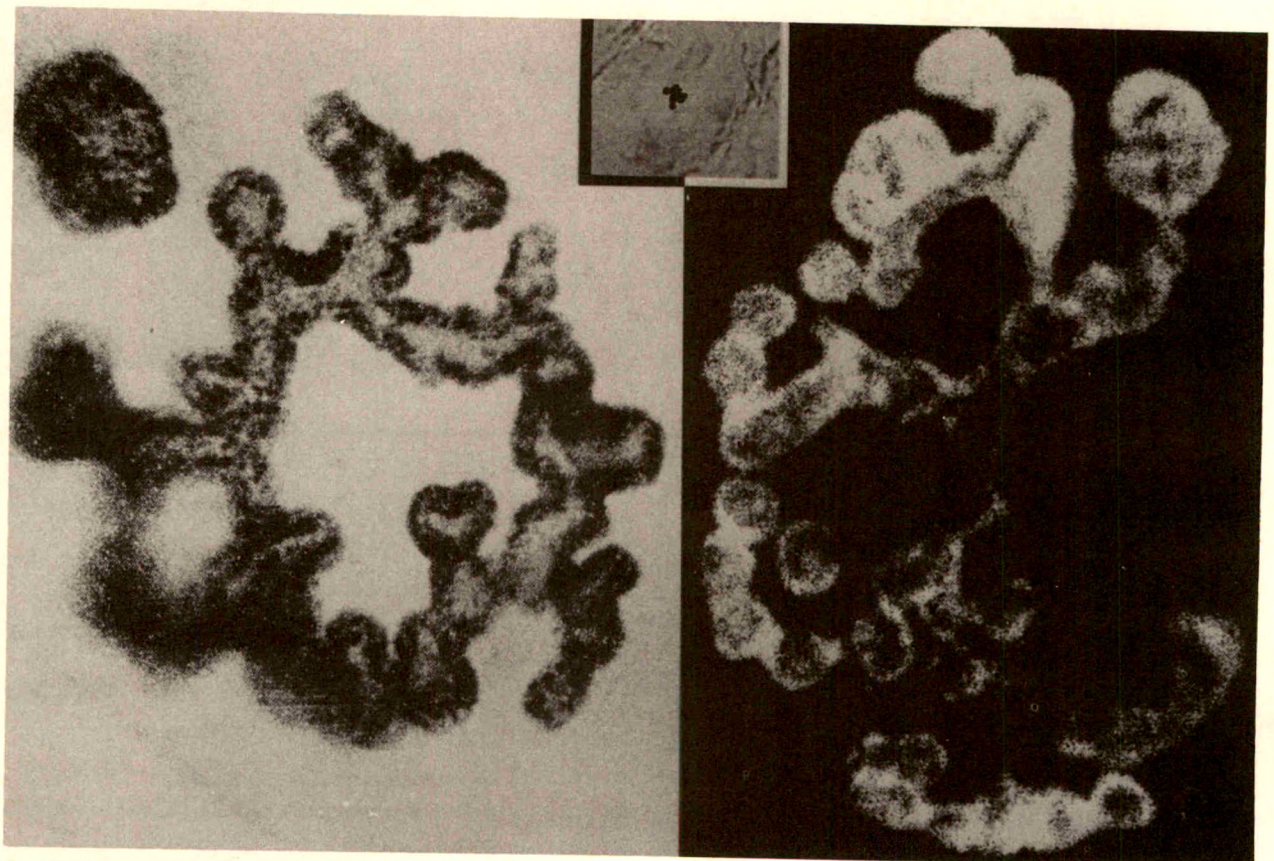


FIG 5. Sequential sections through a neuromuscular junction of rat soleus muscle: inset, low magnification to show location of junction on muscle; others, high magnification of junction; inset and left, histochemical stain for acetylcholinesterase viewed through a light microscope; right, antibody to cAMP coupled to fluorescent label viewed through a dark-field fluorescence microscope.

neuromuscular junction. The resolution of this technique does not permit differentiation between nerve ending and motor end plate, but antibodies to cAMP do not react with end plate regions of preparations in which the nerve is cut and allowed to degenerate. This, and the evidence cited above that cAMP is present and active in the nerve, but not at the end plate, make it seems probable that the cAMP of Fig 5 is in the nerve ending.

The function of cAMP in these nerve endings also has been studied. Signs that it influences the entry of depolarizing ions are described above. Other evidence relates cAMP and release of transmitter. Goldberg and Singer (6, 7) studied dbcAMP and theophylline, applied separately and sequentially, on miniature end plate potentials (mepp) of rat diaphragms in vitro. They reported that both compounds increased the frequency of mepp but did not change their amplitudes or time courses, and that pretreatment with theophylline increased the effect of dbcAMP. Neither dbcAMP nor theophylline changed the resting potential of the end plate. Miyamoto and Breckenridge (9) also saw theophylline increase mepp frequency, without effect on amplitude or time course or end plate resting potential, but did not see any response to dbcAMP or to monobutyryl cAMP until they depolarized the nerve with 15 mM potassium. Although they disagreed over the significance of cAMP in the physiology of neuromuscular transmission, both sets of investigators concluded that the cyclic nucleotide probably promotes the flux of calcium in the nerve ending. Jacobs and McNeice (19) reported that SQ 20,009, a nonxanthine inhibitor of phosphodiesterase, similarly increases mepp frequency.

Fig 6 contains records of mepp activity obtained from experiments in which microelectrodes were placed in the in vivo, in situ cat soleus muscle and dbcAMP was injected intra-arterially (for method see reference 20). Small doses (10 to 50 μg/kg) caused an increase in mepp frequency which could be prevented by prior administration of the calcium channel blocking drug, verapamil. The phosphodiesterase inhibitor SQ 20,009 also caused an increase in frequency, sometimes to very high rates (>200/sec). Neither dbcAMP

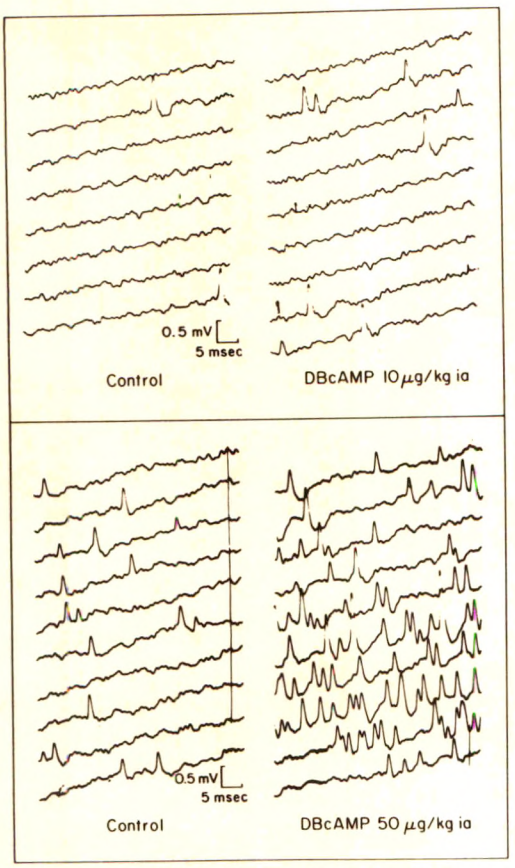


FIG 6. Effect of dbcAMP, 10 and 50 μg/kg on spontaneous miniature end plate potentials in cat soleus muscles. Records are sequential from bottom left to top right of each pair. The two experiments were done in different animals. (Reproduced with permission from Standaert and Dretchen (15)).

nor SQ 20,009 changed mepp amplitude or time course and neither affected the resting potential of the end plate. Curiously, large doses of dbcAMP (50 to 200 μg/kg) caused a decrease in mepp frequency, an observation that may relate to the discrepant reports (6, 7, 9) on the effects of dbcAMP on mepp frequency.

The data on stimulus evoked release are not ambivalent; all investigators agree that dbcAMP and/or phosphodiesterase inhibitors increase quantal content of the evoked end plate potential. Fig 7 contains a record (from Fig 6) of the end plate potential of a rat diaphragm muscle paralyzed by tubocurarine. The addition of 4 M dbcAMP to a preparation exposed to 0.2 mM theophylline increased the end plate potential enough to trigger an action potential from the muscle, i.e., the nucleotide reversed the blockage of transmission induced by the tubocurarine. Since neither dbcAMP nor theophylline changes the end plate's sensitivity to acetylcholine, the increase in end plate potential reflects an increase in transmitter released. Quantiative studies were done by Wilson (21). dbcAMP and theophylline increased not only quantal content, but also the available stores and mobilization of transmitter. Jacobs and McNeice (19) got similar results from the application of SQ 20,009 to rat diaphragms paralyzed by tubocurarine, magnesium, or low calcium.

These demonstrations that phosphodiesterase inhibitors increase the amount of transmitter released by a stimulated nerve are in accordance with several reports (22, 23) that theophylline can antagonize tubocurarine and improve the strength of patients with myasthenia gravis. Just as significant are the data showing that dbcAMP or phosphodiesterase inhibitors increase the size of the available stores and mobilization of transmitter. These indicate that cyclic nucleotides affect processes deep in the cell as well as those at the membrane, and that cAMP may be important to the maintenance of transmitter release from nerves stimulated repeatedly, as in living organisms.

The ion primarily involved in the action of cAMP

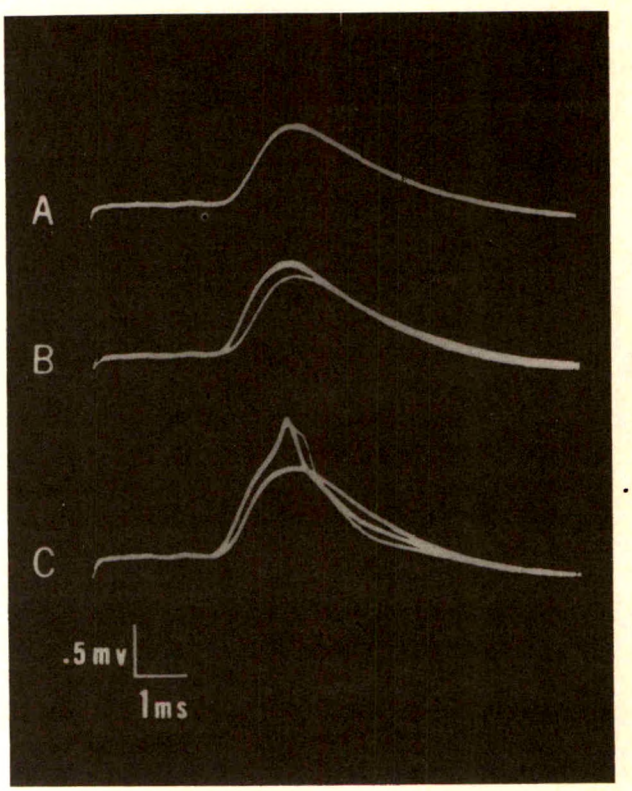


FIG 7. Effects of dbcAMP on end plate potential of rat diaphragm muscle paralyzed by tubocurarine: A, control; B, after 0.2 mM theophyllline; C, after 4 mM dbcAMP. Large spikes in C are muscle action potentials triggered when end plate potential was increased by dbcAMP. (Reproduced with permission from Singer and Goldberg (7)).

has been identified. The basic phenomena, DIA and SBR, indicate depolarization of the nerve ending and might be produced by the influx of either sodium or calcium. Increases in mepp frequency and quantal content commonly are associated with an influx of calcium, and several investigators (6, 7, 9) have concluded that cAMP favors the flow of calcium into the nerve ending. We substantiated this by observing that the neural effects of dbcAMP are not changed by tetrodotoxin, but are attenuated by antagonists of calcium, including verapamil; its methoxy analogue, D-600, manganese, lanthanum, and cobalt. Also, they are diminished when extracellular calcium is lowered by an infusion of 1,2-bis-(2-dicarboxymethylamino-ethoxy)ethane (EGTA) or enhanced when it is raised by infusing $CaCl_2$ (24, 25).

Taken together, these observations led us to the scheme in Fig 8. We postulate that adenylate cyclase in the nerve membrane is activated when an action potential invades the nerve ending. It might be activated directly by the electrical field or, perhaps, because the small amount of calcium that enters with the initial surge of sodium reacts with calmodulin which, in turn, activates the cyclase. Activated adenylate cyclase forms cAMP, which acting via protein kinases causes phosphorylation of other proteins, some of which open channels through which calcium enters the nerve ending. This secondary or late calcium current occurs during the afterpotentials and is related to the release of transmitter. cAMP is destroyed by phosphodiesterase. The scheme postulates a tightly coupled set of reactions, but the postulate is supported by the evidence that lipid-soluble derivatives of cAMP and/or inhibitors of phosphodiesterase prolong afterpotentials and increase the stimulus-evoked release of transmitter, events that occur very rapidly after stimulation of the nerve. The scheme in Fig 8 suggests that in addition to membrane functions cAMP may influence functions inside the cell, including movement of calcium in mitochondria and cytoplasm, the synthesis, storage, and mobilization of transmitter, and certain metabolic systems. These actions would be analogous to those that take place in neurons of the central nervous system and sympathetic nervous systems (26–28). The scheme hints that adenylate cyclase may be related to specific receptors in motor nerve endings.

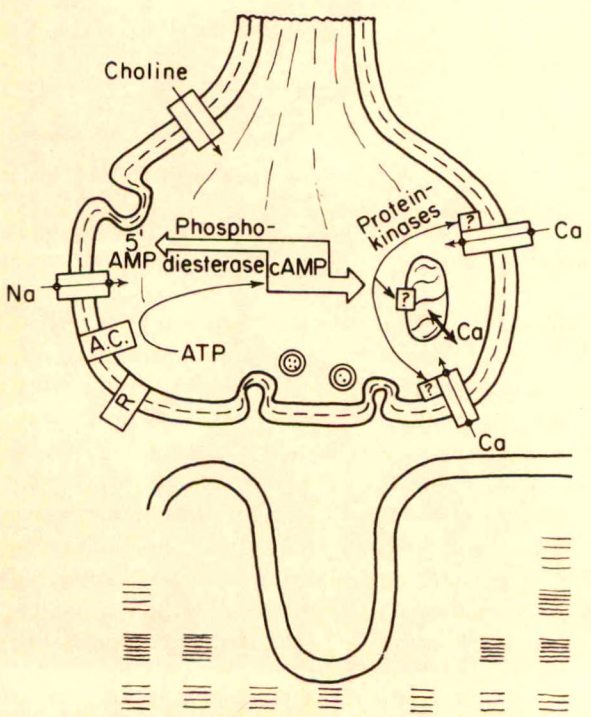


FIG 8. Neuromuscular junction incorporating cyclic nucleotide sequence in relation to calcium channels, mitochondria, vesicles, and prejunctional receptors (R). "?" indicates that specific protein reactant is not known.

The realization that cAMP is involved in the release of transmitter from motor nerves helps explain several phenomena observed in curarized patients. The first was the capacity of azathioprine to antagonize tubocurarine and pancuronium. Fig 9 is a record produced by a patient whose twitch strength had been reduced about 50% by pancuronium. An intravenous injection of azathioprine reversed the blockage of transmission as promptly as an "anticholinesterase" would, but azathioprine is not an inhibitor of cholinesterase and does not have any structural similarities to anticholinesterases. In studying the phenomenon we learned that the neuromuscular effects of azathioprine closely resemble those of theophylline and speculated that azathioprine might inhibit phosphodiesterase. We substantiated this by assaying azathioprine on phosphodiesterase and concluded that azathioprine antagonizes tubocurarine and pancuronium because it inhibits phosphodiesterase, thereby causing cAMP to accumulate in the nerve ending and increase the amount of transmitter released (29). A similar expla-

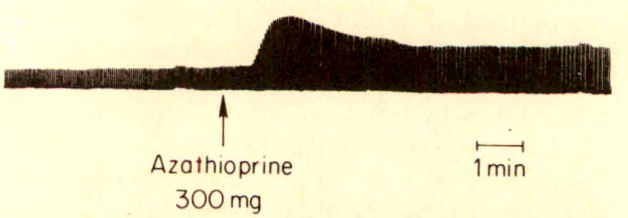


FIG 9. Record of strength of thumb twitch from human being who received azathioprine after pancuronium. Strength was reduced to about 50% of control at beginning of record. (Reproduced with permission from Dretchen et al (29)).

nation has been profferred for the antagonistic interactions between theophylline or aminophylline and tubocurarine or pancuronium (12, 30).

We also have suggested that the increase in neuromuscular blockage produced by furosemide may be related to this compound's capacity to inhibit protein kinases (31). Interestingly, although small doses of furosemide add to the effect of tubocurarine, large doses antagonize the relaxant, apparently because high concentrations of furosemide inhibit phosphodiesterase (18).

Neuromuscular effects of other drugs also may be related to actions on a cyclic nucleotide system in motor nerve endings. Adrenocorticosteroids reduce the efficacy of tubocurarine or pancuronium (32, 33), perhaps because they increase the synthesis of protein kinases and other proteins of the cyclic nucleotide complex (34). Similarly, the effects of phenytoin on neuromuscular transmission have been related to the compound's capacity to depress cyclic nucleotide mediated calcium flux into the nerve ending (35), an effect that may be due to an inhibition by phenytoin of calcium-dependent phosphorylation of proteins (36).

The remarkable similarities among the effects of theophylline and physostigmine led us to compare these two compounds pharmacologically and biochemically. Both produce fasciculations, potentiate the force of stimulated muscles (e.g., Fig 4), antagonize neuromuscular blockage produced by tubocurarine, augment blockage produced by succinylcholine, and increase the response of neuromuscular preparations to dbcAMP (Fig 10). These effects are commonly associated with inhibition of cholinesterase, but theophylline has negligible capacity to inhibit this enzyme. As the similarities in responses to the two drugs cannot be attributed to their inhibitory effects on cholinesterase, we tested the hypothesis that both inhibit phosphodiesterase. Results are shown in Fig 11. Physostigmine inhibits both high and low affinity forms of the soluble and particulate phosphodiesterases extracted from the cat sciatic nerve and is from 5 to 10 times more potent than theophylline in this regard (37). This potency ratio is similar to that for effects on neuromuscular transmission.

This capacity to inhibit phosphodiesterase is not shared by other commonly used anticholinesterases: neostigmine, edrophonium, isoflurophate, or echothiophate. We do not yet know the relative contributions of phosphodiesterase and cholinesterase inhibition to the total action of physostigmine, but there is evidence that physostigmine increases the release

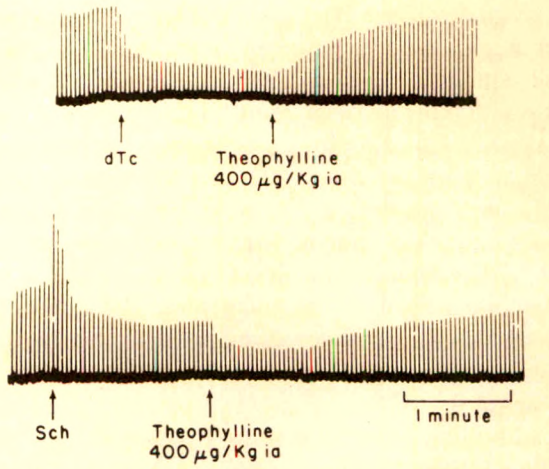


FIG 10. Interaction of theophylline with non-depolarizing and depolarizing muscle relaxants. Cat soleus muscles stimulated supramaximally every 2.5 seconds: top, blockage produced by tubocurarine; bottom, blockage produced by succinylcholine. (Reproduced with permission from Dretchen et al (29)).

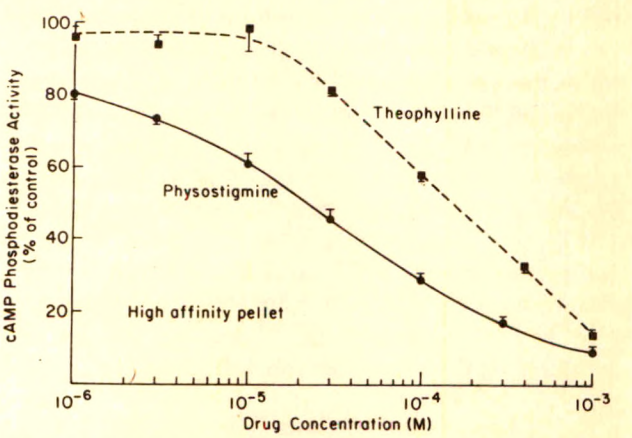


FIG 11. Inhibition of high affinity particulate cAMP phosphodiesterase from cat sciatic nerves by physostigmine and theophylline.

of acetylcholine from motor nerve endings as well as delaying its hydrolysis in the junctional cleft, and this may be due to inhibition of the former enzyme. Even though neostigmine, edrophonium, and other "anticholinesterases" do not inhibit phosphodiesterase, they interact with the cyclic nucleotide system; their neural effects are potentiated by phosphodiesterase inhibitors and blocked by verapamil. The mechanism of these prejunctional actions is not yet known, but seems to be independent of the inhibition of cholinesterase and is not related to an action of acetylcholine on prejunctional receptors.

The special capacity of physostigmine to antagonize depression produced by a variety of anesthetics has been remarked upon frequently. It usually is ascribed to inhibition of cholinesterase and activation of cho-

linergic pathways in the brain (38), even though other cholinergic drugs or anticholinesterases do not produce equivalent results. The discovery of an additional action for physostigmine broadens its spectrum of known activity and suggests that inhibition of phosphodiesterase may be an important component of the drug's action in the central nervous system. This speculation receives support from our finding that tetrahydroaminoacridine (Tacrin), another cholinesterase inhibitor that antagonizes the effects of anesthetics in the central nervous system, also inhibits phosphodiesterase, albeit less effectively than physostigmine.

In the long range, research on cyclic nucleotides and excitation-secretion coupling in motor nerves could lead to new types of muscle relaxants and antagonists. All of the drugs in current use are thought to act principally on the motor end plate and to change transmission by reacting with the receptor or cholinesterase. However, neuromuscular transmission can be blocked as surely by compounds that reduce the release of transmitter and a block can be relieved by compounds that increase the release of transmitter. Examples of the latter are given in Figs 9 and 10 and we have reported that neuromuscular transmission is blocked reversibly by compounds that can reduce cAMP action in nerve endings (7). None of these compounds is suitable for clinical use, but the experiments show that the search for new drugs does not have to be limited to those compounds that act on postjunctional receptors or cholinesterase.

ACKNOWLEDGMENT

The authors thank Dr. T. Phillips for the preparation of Fig 5.

REFERENCES

1. Kebabian JW. Biochemical regulation and physiological significance of cyclic nucleotides in the nervous system. Adv Cyclic Nucleotide Res 1977;8:421–508.
2. Nathanson JA, Greengard P. "Second messengers" in the brain. Sci Am 1977;237:108–19.
3. Standaert FG. Post-tetanic repetitive activity in the cat soleus nerve: its origin, course and mechanism of generation. J Gen Physiol 1963;47:53–70.
4. Standaert FG, Riker WF. The consequences of cholinergic drug actions on motor nerve terminals. Ann NY Acad Sci 1967;144: 517–33.
5. Standaert FG, Dretchen KL, Skirboll LR, Morgenroth VH. The effects of cyclic nucleotides on mammalian motor nerve endings. J Pharmacol Exp Ther 1976;199:544–52.
6. Goldberg AL, Singer JJ. Evidence for a role of cyclic AMP in neuromuscular transmission. Proc Natl Acad Sci USA 1969;64: 134–41.
7. Singer JJ, Goldberg AL. Cyclic AMP and transmission at the neuromuscular junction. Adv Biochem Psychopharmacol 1970;3:335–48.
8. Wilson DF. The effects of dibutyryl cyclic adenosine 3,5-monophosphate theophylline, and aminophylline on neuromuscular transmission in the rat. Clin Pharmacol Ther 1973;188:447–52.
9. Miyamoto MD, Breckenbridge BM. A cyclic adenosine monophosphate link in the catecholamine enhancement of transmitter release at the neuromuscular junction. J Gen Physiol 1974;63:609–24.
10. Krnjevic K, Van Meter WG. Cyclic nucleotides in spinal cells. Can J Physiol Pharmacol 1976;54:416–21.
11. Standaert FG, Dretchen KL, Skirboll LR, Morgenroth VH. A role of cyclic nucleotides in neuromuscular transmission. J Pharmacol Exp Ther 1976;199:553–64.
12. Varagic VM, Zugic M, Mrsulja B. The effect of N-2-dibutyryl adenosine 3′,5′-monophosphate on neuromuscular transmission and concentration of glycogen in the isolated phrenic nerve diaphragm preparation in the rat. Experientia 1972;28: 305–6.
13. Takamori M, Ishii N, Mori M. The role of cyclic 3′5′-adenosine monophosphate in neuromuscular transmission. Arch Neurol 1973;29:420–4.
14. Vapaatalo H. Role of cyclic nucleotides in the nervous system. Med Biol 1974;52:200–7.
15. Standaert FG, Dretchen KL. Cyclic nucleotides and neuromuscular transmission. Fed Proc 1979;38:2183–92.
16. Breckenridge BM, Bray JJ. Cyclic AMP and nerve function. Adv Biochem Psychopharmacol 1970;3:325–33.
17. Horn JP, McAfee DA. Modulation of cyclic nucleotide levels in peripheral nerve without effect on resting or compound action potentials. J Physiol (Lond) 1977;269:753–66.
18. Curley WH, Scappaticci KA, McGee R, Dretchen KL, Standaert FG. Cyclic AMP phosphodiesterases from cat sciatic nerve. Fed Proc 1979;38:272.
19. Jacobs RS, McNeice DM. Motor nerve terminal facilitatory action of SQ 20,009: an inhibitor of cyclic nucleotide phosphodiesterase. J Pharmacol Exp Ther 1977;202:404–10.
20. Hoekman TB, Dretchen KL, Standaert FG. Miniature endplate potentials recorded from mammalian myoneural junction in vivo. Science 1974;183:213–5.
21. Wilson DF. The effects of dibutyryl cyclic AMP, theophylline and aminophylline on neuromuscular transmission in the rat. J Pharmacol Exp Ther 1974;188:447–52.
22. Hashimato Y, Sasaki H, Iwatsuki K. Effect of dibutyryl cyclic AMP on neuromuscular transmission in myasthenia gravis. Tohoku J Exp Med 1976;20:197–8.
23. Brumlik J, Jacobs R, Karzmar AG. Theophylline and myasthenia gravis. Clin Pharmacol Ther 1973;14:380–5.
24. Skirboll LR, Baizer L, Dretchen KL. Evidence for a cyclic nucleotide mediated calcium flux in motor nerve endings. Nature 1977;268:352–4.
25. Skirboll LR, Standaert FG, Dretchen KL. Effects of calcium on a cyclic nucleotide system in soleus motor nerve endings. Eur J Pharmacol 1979;54:295–8.
26. Bloom FE. The role of cyclic nucleotides in central synaptic function. Rev Physiol Biochem Pharmacol 1975;74:1–103.
27. Nathanson JA. Cyclic nucleotides and nervous system function. Physiol Rev 1977;57:158–256.
28. Phillis JW. The role of cyclic nucleotides in the CNS. Can J Neurol Sci 1977;4:153–95.
29. Dretchen KL, Morgenroth VH, Standaert FG, Walts LF. Azathioprine: effects on neuromuscular transmission. Anesthesiology 1976;45:604–9.
30. Doll DC, Rosenberg H. Antagonism of neuromuscular blockade by theophylline. Anesth Analg 1979;58:139–40.
31. Ham J, Scappaticci KA, Dretchen KL, Sohn YJ, Miller RD. Effects of furosemide on neuromuscular transmission. Park Ridge, Il: American Society of Anesthesiologists, 1977:471–2.
32. Laflin MJ. Interaction of pancuronium and corticosteroids. Anesthesiology 1977;47:471–2.
33. Meyers EF. Partial recovery from pancuronium neuromuscular

blockade following hydrocortisone administration. Anesthesiology 1977;46:148–50.
34. Greengard P. Cyclic nucleotides, phosphosylated proteins and the nervous system. Fed Proc 1979;38:2208–17.
35. Dretchen KL, Standaert FG, Raines A. Effects of phenytoin on the cyclic nucleotide system in the motor nerve terminal. Epilepsia 1977;18:337–48.
36. De Lorenzo RJ, Freidman SD. Phenytoin inhibition of neurotransmitter release and protein phosphorylation. Neurology 1978;28:367–8.
37. Curley WH, Dretchen KL, Standaert FG. Inhibition by physostigmine of neural phosphodiesterase. Fed Proc 1980;39:410.
38. Rupreht JR. Physostigmine reversal of diazepam. Anesthesiology 1980;53:180–1.

Calcium Ion Concentration and Beta Adrengeric Activity

The effects of beta adrenergic blockade on calcium-induced alterations in hemodynamic function were studied in intact, halothane-anesthetized dogs. Blood calcium ion concentration [Ca^{2+}], mean arterial (MAP), right atrial, and pulmonary artery balloon-occluded pressures, cardiac output, and heart rate were measured immediately prior to and following rapid intravenous infusion of calcium chloride ($CaCl_2$, 12 mg/kg). Studies were performed both prior to and following beta blockade with propranolol (0.5 mg/kg). An increase in [Ca^{2+}] was associated with increased MAP of short duration without significant alterations in cardiac output, right atrial pressure, or pulmonary artery pressure. Thus, systemic vascular resistance (SVR) was transiently increased. In the presence of beta blockade, administration of the same dose of $CaCl_2$ infused over the same period was associated with a substantially greater increase in [Ca^{2+}]. The hemodynamic response was similar except for a transient increase in cardiac output, recorded 15 seconds after $CaCl_2$ infusion. Fifteen minutes after $CaCl_2$ infusion, recorded hemodynamic variables were not different from control despite persistent elevation of [Ca^{2+}]. Thus the data suggest that calcium bolus infusion is of limited value to increase cardiac output or decrease left ventricular filling pressure (LVFP) in the presence of beta blockade. These data also demonstrate that the effects of calcium bolus infusion are short lived. *(Scheidegger D, Drop LJ: Calcium ion concentration and beta adrenergic activity. J Thorac Cardiovasc Surg 1980;80:441–6).*

Transcutaneous Oxygen Monitoring during Arrest and CPR

The transcutaneous oxygen sensor (tcP_{O_2}), which has been used to predict Pa_{O_2} in neonates, recently has been shown to follow changes in oxygen delivery, rather than Pa_{O_2} during shock and hypoxia in dogs. Six preterminal patients were continuously monitored with tcP_{O_2} and monitored hemodynamically at frequent intervals during cardiac decompensation, arrest, and cardiopulmonary resuscitation (CPR). The weighted mean correlation coefficients between tcP_{O_2} and O_2 delivery as well as between tcP_{O_2} and cardiac output were 0.94 and 0.96, respectively. Five patients died of severe acute respiratory distress syndrome and one patient died intraoperatively of hemorrhagic shock. Four patients were monitored 1 to 7 days before shock occurred. The correlation between tcP_{O_2} and Pa_{O_2} was 0.91 during periods of normal cardiac output in the preterminal period. During cardiac decompensation, the cardiac output, tcP_{O_2} of 25 torr was reached, the tcP_{O_2} fell below the $P\bar{v}_{O_2}$. This also corresponded to a decrease in $\dot{V}_{O_2}$. The mean $\dot{V}_{O_2}$ was 142 ± 24 ml/min·M^2 for tcP_{O_2} values > 25 torr, and 75 ± 15 ml/min·M^2 for tcP_{O_2} < 25 torr ($p < 0.01$). A tcP_{O_2} of >40 torr corresponded to normal cardiac index, O_2 delivery, $\dot{V}_{O_2}$ $P\bar{v}_{O_2}$, and arterial pH (pH_a) while a tcP_{O_2} of <25 torr corresponded to large reductions of these variables. A tcP_{O_2} of <25 torr preceded cardiac arrest by 43± 28 minutes. In summary, tcP_{O_2} correlates: (1) with Pa_{O_2} during hyperoxemia and hypoxemia, (2) with cardiac output during shock, and (3) with O_2 delivery during low flow shock and hypoxemia but not during hyperoxemia or hyperdynamic (high flow) conditions. *(Tremper KK, Waxman K, Bowman R, Shoemaker WC: Continuous transcutaneous oxygen monitoring during respiratory failure, cardiac decompensation, cardiac arrest, and CPR. Crit Care Med 1980;8:377–81).*

REVIEW article

New Concepts in Cardiopulmonary Resuscitation

Judith H. Donegan, MD*

IN 1966, expired air ventilation and closed chest cardiac massage were recommended as the preferred methods for performing cardiopulmonary resuscitation (CPR) by the Ad Hoc Committee on Cardiopulmonary Resuscitation of the National Research Council (1, 2). At that time, steps A (airway), B (breathing), C (circulation), and D (definitive therapy) were delineated. In 1973, the American Heart Association and the National Academy of Sciences-National Research Council sponsored a National Conference on Cardiopulmonary Resuscitation and Emergency Cardiac Care (ECC) at which national standards for the performance of CPR were developed (3). Since that time there has been a great amount of interest in teaching and learning CPR; a 1977 Gallup poll showed that more than 12 million people had been trained in the technique. Results obtained from research and practical experience indicated that certain aspects of the standards required updating. Accordingly, a national conference was held in September 1979, to make the necessary changes, and the new guidelines were published in 1980 (4). This review discusses areas in which changes are being made, as well as the literature supporting these changes.

The effectiveness of bystander CPR has been well documented (5–8). One study (5), conducted in a large metropolitan area, demonstrated that institution of basic life support (BLS) by trained lay persons within 5 minutes of the occurrence of cardiopulmonary arrest contributed significantly to an increase in survival rate, as well as increased quality of survival. In a study (8) that investigated the relative importance of various time-related parameters upon hospital discharge rate in victims of out-of-hospital cardiopulmonary arrest, two critical time periods were identified: (*a*) the time from occurrence of cardiac arrest to the initiation of CPR (usually BLS provided by a bystander); and (*b*) the time from occurrence of arrest to the provision of advanced cardiac life support (ACLS). Those patients whose resuscitation was initiated within 4 minutes of arrest and who received definitive care (ACLS) within 8 minutes had the highest rate of discharge from the hospital (43%).

Airway Management and Ventilation

Opening Airway

Methods for opening the airway of an unconscious victim are aimed at relieving obstruction due to the tongue. These include the head tilt-neck lift and the jaw thrust maneuvers outlined in the standards published in 1974 (3). A study in 1976 (9) compared these two methods, in anesthetized patients, with a head tilt-chin lift technique. The chin lift and jaw thrust techniques were superior to the neck lift method both in (*a*) anesthetized patients who were apneic and receiving mouth-to-mouth ventilation, and (*b*) in anesthetized patients who were completely obstructed, but were making spontaneous respiratory efforts. In the former group, the subjective evaluation of the anesthesiologist performing mouth-to-mouth ventilation was that 91% had a good airway with the chin lift method, 78% with the jaw thrust method, and only 39% when neck lift was employed. All subjects with obstructions had their airways opened by each of the three methods, and tidal volumes were measured by a spirometer attached to an anesthesia mask. As shown in Fig 1, with the neck lift method, tidal

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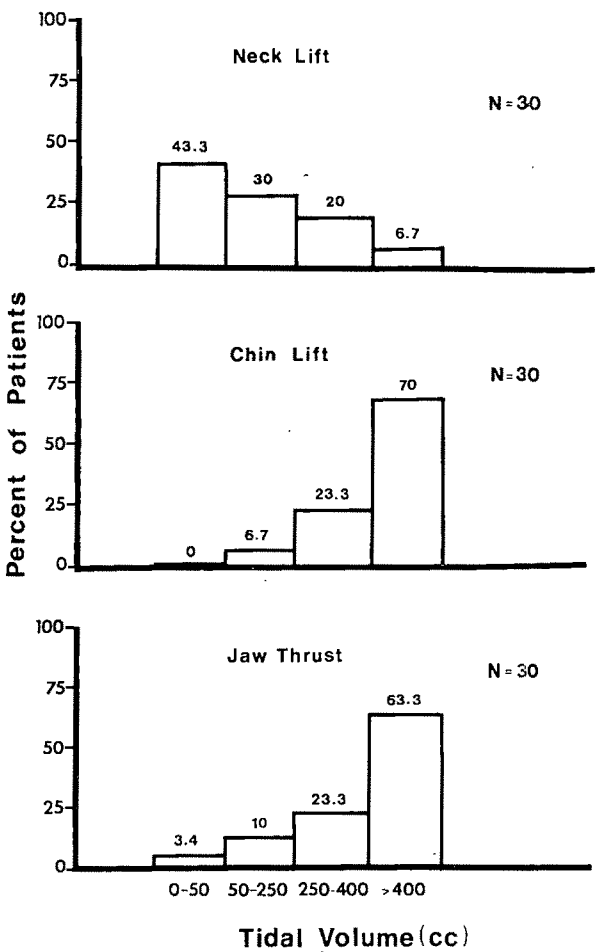


FIG 1. Comparison of effectiveness of three methods for opening airway in obstructed anesthetized patients making spontaneous respiratory efforts. (Adapted from Guildner (9) and reproduced with permission from: Donegan J. Cardiopulmonary resuscitation. In: Miller RD, ed. Anesthesia. New York: Churchill-Livingstone, in press 1981.)

volumes greater than 400 ml were obtained in only 6.7% of the cases. In contrast, with the jaw thrust and chin lift methods, volumes greater than 400 ml were obtained in 63% and 70% of the cases, respectively. The chin lift and jaw thrust methods pull the lower jaw, and along with it the tongue, forward, probably accounting for the superiority of these two methods over that of neck lift. However, neck lift has been taught to millions of people, and it does work. All three methods are recognized, and if all are taught, the individual performing basic life support can utilize whichever one works best in a given situation.

Management of Obstructed Airway

Recommendations for clearing foreign body airway obstruction, which appeared in the 1974 standards (3), included back blows and finger probes of the throat. In 1974, Heimlich (10) proposed the use of an abdominal thrust maneuver for relieving airway obstruction. Guildner et al (11) found that manual thrusts applied to the mid- or lower chest produced slightly better volumes, peak flows, and airway pressures than did thrusts applied to the abdomen. Controversy ensued over which of these two methods is better and whether back blows are helpful or harmful. Reports from individuals who had experience in the treatment of foreign body airway obstruction with various methods were collected by the American Heart Association and tabulated recently in an article by Redding (12). Maneuvers used included back blows, chest thrusts, abdominal thrusts (Heimlich maneuver), finger probes, CPR, and the utilization of instrumentation such as suction equipment and endoscopy. Data were compiled from 225 cases, in 116 of which only one method was used and was successful. In 104 cases more than one method was tried; in 75 of these one method was successful after others had failed, whereas in 29 instances the rescuer felt that a combination of methods was successful. For each of the maneuvers both successes and failures were described. It appears that the current recommendation of utilizing a combination of back blows, abdominal and/or chest thrusts, followed by a finger probe for the unconscious victim, is sound. The current guidelines state that "the sequence of thrusts followed by back blows could represent an acceptable alternative to the recommended sequence of back blows followed by thrusts" (4).

Ventilation, Oxygenation, and Airway Control

Expired air ventilation is a technique that can be applied rapidly, does not require adjunctive equipment, and, if performed properly, provides good alveolar ventilation. However, the F_{IO_2} that can be delivered is low (0.16 to 0.17), and no means of preventing gastric distension is available. The previous recommendation for relieving gastric distension was to "exert moderate pressure over the victim's epigastrium. . ." (3). It is recognized that this technique may be hazardous, leading almost certainly to regurgitation of stomach contents; the recommendation now is that this maneuver not be performed, either in adults or children, unless gastric distension is sufficiently severe to cause ineffective ventilation (4).

The best method of airway control remains the endotracheal tube (cuffed in adults). In many areas paramedical personnel are trained in this technique and perform intubation in the field. In other areas these personnel use, instead, the esophageal obturator

airway (Fig 2), which may be inserted blindly. A recent modification of the esophageal obturator airway is the esophageal gastric tube airway (13) (Fig 2, B). This modification allows the passage of a #16 gastric tube into the stomach and the application of suction while ventilation proceeds. When either of these devices is used, an endotracheal tube should be placed before the esophageal tube is removed, as its removal often leads to regurgitation.

Cardiac Resuscitation

Closed Chest Cardiac Compression

The importance of equal time for compression and relaxation during cardiac massage was examined in a study reported in 1977 (14). Resuscitation was begun using manual external cardiac compression, and within 30 minutes this was replaced by a pneumatic piston, computer-driven, compression device in which the rate and duration of compression could be altered independently without interrupting chest compression. Direct radial artery pressures, as well as transcutaneous carotid or femoral artery flow velocities, were measured. Optimum flows were found when compression duration was 50% to 60% of the cycle length. When these prolonged compression durations were maintained, variations in rate of compression (i.e., 40, 60, and 80/min) had little effect on flow. The authors stressed that in order to perform compression correctly, the rescuer must make a distinct pause at the point of maximal compression. This is the reason for the warning against quick, bouncing, or jabbing compressions which is stressed in CPR training.

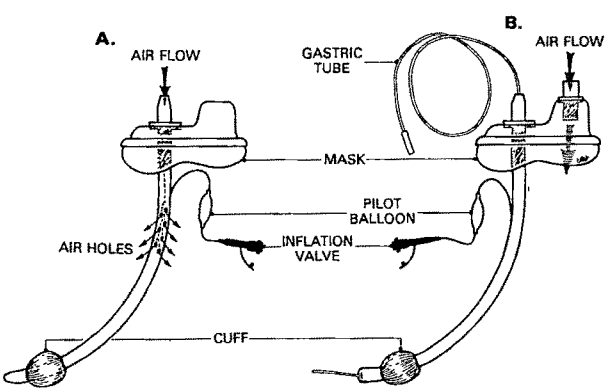


FIG 2. Esophageal obturator airway (A) and esophageal gastric tube airway (B). (Reproduced with permission from: Donegan J. Cardiopulmonary resuscitation. In: Miller RD, ed. Anesthesia. New York: Churchill-Livingstone, in press 1981.)

New investigations are adding to the knowledge of the mechanism of blood flow during closed chest cardiac massage (15–17). The classic explanation is the one proposed by Kouwenhoven and colleagues (18), namely, that blood flow results from a direct compression of the heart between the sternum and the spine. More recent evidence (15) indicates that the increase in intrathoracic pressure that results from compression of the chest may be an equally important factor. This increase in pressure is reflected as an equal elevation of pressure in the cardiac chambers and in the intrathoracic great vessels; however, it is transmitted unequally to the extrathoracic arterial and venous systems. Due to venous collapse secondary to the high intrathoracic pressure, there is a smaller increase in pressure in the extrathoracic venous system than in the extrathoracic arterial system. Thus, an arteriovenous pressure gradient is created, with resultant antegrade blood flow during compression. During relaxation, the intrathoracic pressure decreases below venous pressure, and blood flows from the extrathoracic veins into the right heart. Other evidence supporting this mechanism includes the study of Criley and associates (19), which showed that patients who developed acute ventricular fibrillation during coronary angiography maintained adequate arterial pressure and remained conscious without external cardiac massage if they coughed repeatedly. The authors have recently verified this finding in both clinical and experimental settings (20).

Coordination of Ventilation and Cardiac Massage

Following their classic paper on the technique of external cardiac massage, Jude and colleagues (18) published their experience with CPR in patients using the "independent" technique for ventilation and cardiac massage (21). This meant 60 compressions and 16 ventilations per minute, with no attempt by the two rescuers to coordinate their efforts. At the same time, Safar et al (22) advocated the "alternating" technique, using four sternal compressions to one ventilation. Wilder and associates (23) compared these two techniques in dogs in relation to their ability to maintain blood pressure and blood flow, as well as their effect on survival. They found that the independent and the alternating methods produced virtually identical results. A "simultaneous" technique was also studied in which a mechanical ventilator was set to deliver 56 breaths per minute and the sternum was compressed each time the chest began to expand. Systolic blood pressure, blood flow, and survival were all better with this method than with any other.

Harris, Kirimli, and Safar (24) compared the simultaneous technique with an alternating technique in which a ratio of 15:2 was used for one rescuer and a ratio of 5:1 for two rescuers. They found carotid blood flows and arterial pressures obtained with the two methods identical, whereas ventilation was better with the alternating technique. Their technique and the ratios that they recommended have become the standard (3, 4).

A group of investigators at The Johns Hopkins University has reexamined the question of the best method of coordinating ventilation and cardiac compression in light of their findings concerning the importance of increased intrathoracic pressure as a mechanism for blood flow during CPR. They have introduced "new CPR" (17) (i.e., compressions at a rate of 40/min with a 60% compression duration, and simultaneous ventilation at airway pressures from 60 to 110 cm H_2O). They found that this method increased systolic pressure about 13 mm Hg and carotid blood flow 113% to 643% over conventional CPR. The authors stress, however, that "further studies of potential complications and long-term effects of new CPR, particularly on adequacy of ventilation, are needed before clinical implementation is undertaken" (17).

Hodgkin et al (25) studied the effects of positive end-expiratory pressure and an increased frequency of ventilation (3:1) on arterial pressure, blood flow, and blood gases. They found that arterial oxygenation was significantly improved with PEEP and that arterial carbon dioxide levels were significantly lower when a 3:1 ratio was used rather than the conventional 5:1. However, arterial pressure and carotid flow were lower when either PEEP or an increased ventilation frequency were used, probably because both of these methods interfere with venous return to the heart. These findings are identical with those reported by Wilder et al (23), who, in addition to comparing the independent, alternating, and simultaneous methods of coordinating compression and ventilation, also studied a group of dogs in which a constant airway pressure was maintained while compressions were performed. This group had the lowest blood pressure, blood flow, and survival rate. The constant airway pressure technique should not be confused with new CPR. In new CPR, positive airway pressure is applied only during sternal compression, not during the relaxation phase.

Babbs et al (26) showed, in dogs, that when a breath was interposed after every five compressions at high airway pressures (e.g., 20 to 50 cm H_2O), pH was in the normal to alkalotic range, Pa_{CO_2} was low, oxygenation was adequate, and no change in cardiac output occurred.

For the present, these findings do not call for a change in the teaching of the manner in which ventilation and compression are coordinated during CPR.

Precordial Thump

The place of the precordial thump in CPR is now reserved for two specific monitored situations: (a) early onset ventricular tachycardia or ventricular fibrillation, and (b) ventricular asystole due to complete heart block in which rhythmic thumps produce a QRS complex and associated cardiac contraction. In this case it may be used until a pacemaker can be inserted. The precordial thump is not recommended for pediatric patients.

Defibrillation

Defibrillation is well established as the definitive therapy for ventricular fibrillation, but controversy has existed over what factors influence the success of defibrillation and what the correct energy levels should be. Factors that have been investigated regarding their influence upon successful defibrillation include the duration of fibrillation (27, 28), the condition of the myocardium (27, 29), heart size (27, 30), body weight (27, 31, 32), paddle size (33), and whether or not previous countershocks were applied (34). The relative importance of two factors, the duration of ventricular fibrillation and the condition of the myocardium, led to controversy over whether defibrillation should be attempted as soon as fibrillation was recognized or whether the attempt should be postponed until drug therapy to combat hypoxia and acidosis was instituted. Yakaitis and associates (29) found no difference in defibrillation success between dogs that were severely hypoxic and acidotic and those that were not, whereas the incidence of successful defibrillation was inversely proportional to the duration of fibrillation. Kerber and Sarnat (27) investigated the effects of body weight, heart weight, hypoxia, acidosis, and delay before defibrillation. The most important factor relating to success was a short delay before defibrillation.

Controversy also exists concerning the correct energy levels for defibrillation (35). Some investigators (31) found an inverse relationship between success rate and body weight, and suggested that the energy output of conventional defibrillators might be inadequate for heavy subjects. Others reported high success

rates with conventional dosages, even in patients weighing more than 90 kg (36, 37). Current recommendations for defibrillation are: (*a*) it should be attempted immediately if the onset of fibrillation is monitored or the victim has been in arrest less than 2 minutes; and (*b*) for the victim in arrest for an undetermined period, defibrillation should be administered only after BLS has been performed for at least 2 minutes (4). The initial energy level should be 200 to 300 joules in either case. If the first shock is unsuccessful, a second may be delivered at the same energy level. If more than two attempts at defibrillation are required, adequacy of oxygenation should be reassessed, epinephrine given, and further shocks delivered at a dosage of 360 joules.

Drug Therapy

The major changes in drug therapy for cardiac resuscitation have occurred in the areas of the antiarrhythmics, sodium bicarbonate, and the use of the endotracheal route for drug administration. Drugs that are effectively absorbed from the tracheobronchial tree include epinephrine (38–42), lidocaine (41–43), atropine (41), and isoproterenol (42). This makes early intubation very advantageous, as it can often be accomplished more rapidly than can the establishment of an intravenous line.

There is evidence that sodium bicarbonate has been used overzealously during CPR (44, 45). Bishop and Weisfeldt (45) showed in animal experiments that, if acidosis was not present before arrest, pH could be kept normal for several minutes without bicarbonate if adequate ventilation was provided. The deleterious effects of excessive $NaHCO_3$ administration include hypercarbia, hypernatremia, hyperosmolality, and metabolic alkalosis. The decision to administer bicarbonate ideally should be based upon information obtained from measurements of arterial blood gas tensions and pH. If these cannot be obtained, the physician should use judgment as to when bicarbonate is needed based upon the length of time the victim has been in cardiac arrest. When bicarbonate is given without blood gas information, the initial dose should be 1 meq/kg, followed by 0.5 meq/kg every 10 minutes of continued arrest.

Among antiarrhythmic drugs, lidocaine remains the drug of first choice. Its onset of action is rapid and its duration is short (15 to 20 minutes following an intravenous bolus) (46). In clinically employed doses it has minimal effects upon myocardial contractility (47) and systemic arterial pressure. Therapeutic blood levels of lidocaine (1.5 to 6.0 μg/ml) are most rapidly obtained and adequately maintained with the use of an intravenous bolus followed by a constant infusion. A new technique for lidocaine administration, which may be used as an alternative to the standard method of a 1-mg/kg bolus followed by an infusion of 1 to 4 mg/min, has been introduced by Wyman and colleagues (48). This consists of a 75-mg bolus and the simultaneous institution of a 2-mg/min infusion. For recurrent ventricular ectopy a 50-mg bolus may be given every 5 minutes to a total dose of 225 mg. With each additional bolus the infusion rate is increased 1 mg/min, to a maximum rate of 4 mg/min.

Procainamide may effectively suppress ventricular ectopy when lidocaine does not. The drug is given, during continuous electrocardiographic and arterial pressure monitoring, in a dose of 100 mg every 5 minutes, at a rate of 20 mg/min (49), until one of the following occurs: (*a*) the dysrhythmia is suppressed; (*b*) hypotension occurs; (*c*) the QRS is widened by 50% of its original width; or (*d*) a total of 1 g is given. Procainamide may be given as an infusion at a rate of 1 to 4 mg/min. Therapeutic blood levels range from 4 to 8 μg/ml (50).

Bretylium tosylate, a quaternary ammonium compound with antiarrhythmic properties, is new to the CPR drug therapy armamentarium. Its mechanism of action is not well understood, although it is known to have both autonomic (51, 52) and membrane-active (53) effects. Bretylium may be effective in treating resistant ventricular dysrhythmias when lidocaine, procainamide, and multiple attempts at defibrillation have failed (54). The initial intravenous dose in adults is 5 mg/kg, followed by attempted defibrillation. If fibrillation persists, additional doses of 10 mg/kg every 15 to 30 minutes to a total of 30 mg/kg may be given. Bretylium may also be administered as a constant infusion at a rate of 1 to 2 mg/min.

Resuscitation of Infants and Children

This important aspect of CPR has been addressed by a special task force designated by the American Heart Association as the Working Group on CPR and ECC in Infants and Children. The age groups under consideration have been defined as: newborn (less than 1 month old), infant (less than 1 year), child (1 to 8 years), and adult (more than 8 years). The variations in the techniques of expired air ventilation, closed chest massage, and obstructed airway management as they pertain to the infant and child are listed in Table 1.

It should be noted that in the management of foreign body airway obstruction, abdominal thrusts

TABLE 1
Resuscitation Technique for Infants and Children

	Infants	Children
Age	<1 year	1–8 years
Ventilation		
Method	Mouth-to-mouth and nose	Mouth-to-mouth and nose Mouth-to-mouth
Rate	20/min	15/min
Management of foreign body airway obstruction	Back blows and chest thrusts; abdominal thrusts are not recommended	Back blows and chest thrusts; abdominal thrusts are not recommended
Where to check pulse	Brachial artery at mid-upper arm	Carotid artery
Compression		
Method	2–3 fingers on mid-sternum (BLS); encircle chest and use thumbs to compress (ACLS)	3 fingers for small child; heel of one hand for larger child
Depth	½–1 in	1–1½ in
Rate	100/min	80/min
Compression/ventilation ratio	5:1	5:1

are not recommended for infants and children as the potential for liver trauma is high in pediatric patients. Back blows should be delivered with the infant straddled over the rescuer's arm, with the head lower than the trunk. If the victim is a child who is too large for this position, the rescuer kneels on the floor and drapes the victim across his thighs, keeping the head of the victim lower than the trunk. Blind finger probes are considered dangerous for use in infants and children as they may push the foreign body in more deeply. Instead of the finger probe following the chest thrusts in an unconscious victim, the rescuer's thumb is placed in the victim's mouth over the tongue, the lower jaw is lifted forward, and the mouth is opened. If the foreign body is visualized at this time, it is removed.

Where to Check Pulse

The Working Group on CPR in infants and children has determined that in a fairly large percentage of normal, sleeping infants the precordial pulse, previously the pulse recommended to check for diagnosing cardiac arrest in this age group (3), is not palpable. The most readily palpable pulse in infants appears to be the brachial artery at the mid-upper arm.

Closed Chest Cardiac Massage

The superiority of a chest encircling technique of cardiac compression for infants over that of the standard two-finger technique has been demonstrated (55, 56). This method consists of encircling the infant's chest with the rescuer's hands and using the thumbs for cardiac compression. Todres and Rogers (55) obtained higher systolic pressures with the chest encircling technique than with the two-finger method; Thaler and Stobie (56) found that maintenance of adequate systolic pressures required less externally applied pressure when the chest-encircling technique was utilized. Currently this technique is the preferred method for closed chest cardiac massage in newborns during ACLS (4).

Drugs and Defibrillation

The dosages of the principal drugs used for cardiac resuscitation of infants and children are listed in Table 2.

Recommendations regarding energy levels and paddle size for defibrillation in the pediatric group have been made by the Target Activity Group (57). Paddles of 4.5 cm in diamater are suitable for infants, and those of 8 cm in diameter for children. For the initial defibrillation attempt, an energy level of 2 joules/kg should be selected; if this attempt is unsuccessful, a second should utilize twice the initial energy (i.e., 4 joules/kg). Gutgesell and associates (58) demonstrated that energy levels required for defibrillation in the pediatric age group were directly related to body weight, and 89% of the attempts were successful when a dose of 2 joules/kg was utilized. In those in whom the initial attempt was unsuccessful, fibrillation was terminated with 4 joules/kg or less.

Postresuscitation Management

Once an organized cardiac rhythm and acceptable blood pressure are restored, the phase of postresuscitation management is entered. This phase is as important to the patient's outcome as was the resuscitation effort and must be pursued with the same enthusiasm. A complete review of measures to be taken in the postresuscitation period is beyond the scope of the present material, and only a few aspects

TABLE 2
Recommended Drug Dosages for Resuscitation of Infants and Children

Drug	Infants	Children
Atropine (mg/kg)	0.03	0.02
Bicarbonate (meq/kg)	2	1
Calcium chloride (10%) (ml/kg)	0.3	0.25
Epinephrine (1:10,000) (ml/kg)	0.1	0.1
Lidocaine (mg/kg)	0.5	1
Isoproterenol (μg/kg min initially)	0.1	0.1
Dopamine (μg/kg/min)	2–10	2–10

of this important and rapidly evolving area are mentioned here. For more information the reader is referred to reviews by Safar et al (59, 60) and to the new *Standards and Guidelines for CPR and ECC* (4).

Continuing intensive care and pharmacologic support as needed will be required for even the patient who responded immediately to resuscitation. The victim who has single or multiple system failure following CPR must be provided with treatment and supportive care, as is any patient with failure of one or more systems. In addition, if the arrest was associated with ventricular fibrillation or ventricular tachycardia, a lidocaine infusion is maintained for 12 to 24 hours.

Approximately 20% of long-term survivors of cardiac arrest sustain permanent brain damage (61). Neurologic syndromes range in severity from mild psychologic disturbances to amnesia, corticol blindness and seizures resulting from focal damage, to brain death resulting from global structural damage, (62).

The best method for resuscitation of the brain that has received an anoxic-ischemic insult is the subject of intense research activity at the present time. Measures currently felt to be efficacious in this context are: (*a*) maintenance of arterial pressure at normal levels, (63–67) and (*b*) prevention of increased intracranial pressure by mild hyperventilation (Pa_{CO_2} 28 to 32 torr), diuretic therapy, avoidance of hyperthermia, and the elevation of the head 30 degrees to increase cerebral venous drainage (59). Maintenance of normal arterial pressure is particularly important. Both hypotension (63) and severe hypertension (64) in the postarrest period have been associated with a poor neurologic outcome, whereas normotension has been shown to promote reflow (65–67) and improve outcome (63, 64, 67).

A great deal of investigation is currently underway assessing the possible efficacy of barbiturate therapy for cerebral resuscitation. Some investigators (68–70) have reported good results, whereas others (71) failed to find that such therapy improved neurologic recovery. Clinical feasibility trials of the use of barbiturates in brain resuscitation were carried out in 1976–1977 (72), and a prospective, multi-institutional study has been initiated. Immobilization and controlled ventilation were shown by Bleyaert and colleagues (73) to reduce neurologic deficit in a monkey model of global brain ischemia, and the question of how much of the barbiturate effect may be due to its enhancement of these measures has been raised. Other suggested mechanisms for a possible protective effect of barbiturates have been reviewed by Safar et al (59), and include: (*a*) reduction of cerebral metabolism combined with improvement of reperfusion, (*b*) prevention of lipid peroxidation by scavenging of free radicals, (*c*) reduction of intra- and extracellular edema, (*d*) suppression of convulsive hyperactivity, and (*e*) reduction of intracranial pressure.

Conclusion

Knowledge regarding the principles and practices of CPR is constantly expanding as research and practical experience in the techniques are pursued. As with other areas of medicine, recommendations regarding standards of practice will continue to be updated as necessary to keep pace with this knowledge.

ACKNOWLEDGMENTS

The author wishes to express her thanks to William Donegan, MD, and David Webb, MD, for reviewing the manuscript, and to Carol Couturier and Linda Faustmann for typing it.

REFERENCES

1. The Ad Hoc Committee on Cardiopulmonary Resuscitation of the Division of Medical Sciences, National Academy of Sciences-National Research Council. Cardiopulmonary resuscitation. JAMA 1966;198:372–9.
2. Gordon AS, ed. Cardiopulmonary Resuscitation Conference Proceedings, May 23, 1966, Washington, DC, National Academy of Sciences-National Research Council, 1967 (Publication no 1494).
3. Standards for cardiopulmonary resuscitation (CPR) and emergency cardiac care (ECC). JAMA 1974;227 (Suppl 7):833–68.
4. Standards and guidelines for cardiopulmonary resuscitation (CPR) and emergency cardiac care (ECC). JAMA 1980;244:453–509.
5. Copley DP, Mantle JA, Rogers WJ, Russell RO Jr, Rackley CE. Improved outcome for prehospital cardiopulmonary collapse with resuscitation by bystanders. Circulation 1977;56:901–5.
6. Lund I, Skulberg A. Cardiopulmonary resuscitation by lay people. Lancet 1976:2:702–4.
7. Thompson RG, Hallstrom AP, Cobb LA. Bystander-initiated cardiopulmonary resuscitation in the management of ventricular fibrillation. Ann Intern Med 1979;90:737–40.
8. Eisenberg MS, Bergner L, Hallstrom A. Cardiac resuscitation in the community: importance of rapid provision and implications for program planning. JAMA 1979;241:1905–7.
9. Guildner CW. Resuscitation—opening the airway: a comparative study of techniques for opening an airway obstructed by the tongue. JACEP 1976;5:588–90.
10. Heimlich HJ. Pop goes the café coronary. Emerg Med 1974;6: 154–5.
11. Guildner CW, Williams D, Subitch T. Airway obstructed by foreign material: the Heimlich maneuver. JACEP 1976;5:675–7.
12. Redding J. The choking controversy: critique of evidence on the Heimlich maneuver. Crit Care Med 1979;7:475–9.
13. Gordon AS. Improved esophageal obturator airway (EOA) and new esophageal gastric tube airway (EGTA). In: Safar P, Elam JO, eds. Advances in cardiopulmonary resuscitation. New York: Springer-Verlag, 1977:58–64.
14. Taylor GJ, Tucker WM, Greene HL, Rudikoff MT, Weisfeldt ML. Importance of prolonged compression during cardiopulmonary resuscitation in man. N Engl J Med 1977;296:1515–7.
15. Rudikoff MT, Maughan WL, Effron M, Freund P, Weisfeldt

ML. Mechanisms of blood flow during cardiopulmonary resuscitation. Circulation 1980;61:345–52.
16. Babbs CF. New versus old theories of blood flow during CPR. Crit Care Med 1980;8:191–5.
17. Chandra N, Rudikoff M, Weisfeldt ML. Simultaneous chest compression and ventilation at high airway pressure during cardiopulmonary resuscitation. Lancet 1980;1:175–8.
18. Kouwenhoven WB, Jude JR, Knickerbocker GG. Closed chest cardiac massage. JAMA 1960;173:1064–7.
19. Criley JM, Blaufuss AH, Kissel GL. Cough-induced cardiac compression: self-administered form of cardiopulmonary resuscitation. JAMA 1976;236:1246–50.
20. Niemann JT, Rosborough J, Hausknecht M, Brown D, Criley JM. Cough-CPR. Documentation of systemic perfusion in man and in an experimental model: a "window" to the mechanism of blood flow in external CPR. Crit Care Med 1980;8:141–6.
21. Jude JR, Kouwenhoven WB, Knickerbocker GG. Cardiac arrest. JAMA 1961;178:1063–70.
22. Safar P, Brown TC, Holtey WJ, Wilder RJ. Ventilation and circulation with closed chest cardiac massage in mar.. JAMA 1961;176:574–6.
23. Wilder RJ, Weir D, Rush BF, Ravitch MM. Methods of coordinating ventilation and closed chest cardiac massage in the dog. Surgery 1963;53:186–94.
24. Harris LC, Kirimli B, Safar P. Ventilation-cardiac compression rates and ratios in cardiopulmonary resuscitation. Anesthesiology 1967;28:806–13.
25. Hodgkin BC, Lambrew CT, Lawrence FH, Angelakos ET. Effects of PEEP and of increased frequency of ventilation during CPR. Crit Care Med 1980;8:123–6.
26. Babbs CF, Voorhees WD, Fitzgerald KR, Holmes HR, Geddes LA. Influence of interposed ventilation pressure upon artificial cardiac output during cardiopulmonary resuscitation in dogs. Crit Care Med 1980;8:127–30.
27. Kerber RE, Sarnat W. Factors influencing the success of ventricular defibrillation in man. Circulation 1979;60:226–30.
28. Yakaitis RW, Ewy GA, Otto CW, Taren DL, Moon TE. Influence of time and therapy on ventricular defibrillation in dogs. Crit Care Med 1980;8:157–63.
29. Yakaitis RW, Thomas JD, Mahaffey JE. Influence of pH and hypoxia on the success of defibrillation. Crit Care Med 1975;3: 139–42.
30. Tacker WA Jr, Guinn GA, Geddes LA, Bourland JD, Korompai FL, Rubio PA. The electrical dose for direct ventricular defibrillation in man. J Thorac Cardiovasc Surg 1978;75:224–6.
31. Tacker WA Jr, Galioto FM Jr, Giuliani E, Geddes LA, McNamara DG. Energy dosage for human transchest electrical ventricular defibrillation. N Engl J Med 1974;290:214–5.
32. Gascho JA, Crampton RS, Cherwek ML, Sipes JN, Hunter FP, O'Brien WM. Determinants of ventricular defibrillation in adults. Circulation 1979;60:231–40.
33. Thomas ED, Ewy GA, Dahl CF, Ewy MD. Effectiveness of direct current defibrillation: role of paddle electrode size. Am Heart J 1977;93:463–7.
34. Geddes LA, Tacker WA, Cabler P, Chapman R, Rivera R, Kidder H. The decrease in transthoracic impedance during successive ventricular defibrillation trials. Med Instrum 1975;9: 179–80.
35. Lown B, Crampton RS, DeSilva RA, Gascho J. The energy for ventricular defibrillation—too little or too much? N Engl J Med 1978;298:1252–3.
36. Gascho JA, Crampton RS, Sipes JN. Energy levels and patient weight in ventricular defibrillation. JAMA 1979;242:1380–4.
37. Campbell NPS, Webb SW, Adgey AAJ, Pantridge JF. Transthoracic ventricular defibrillation in adults. Br Med J 1977;2: 1379–81.
38. Redding JS, Asuncion JS, Pearson JW. Effective routes of drug administration during cardiac arrest. Anesth Analg 1967;46: 253–8.
39. Roberts JR, Greenberg MI, Knaub M, Baskin SI. Comparison of the pharmacological effects of epinephrine administered by the intravenous and endotracheal routes. JACEP 1978;7:260–4.
40. Roberts JR, Greenberg MI, Knaub M, Kendrick ZV, Baskin SI. Blood levels following intravenous and endotracheal epinephrine administration. JACEP 1979;8:53–6.
41. Elam JO. The intrapulmonary route for CPR drugs. In: Safar P, Elam JO, eds. Advances in cardiopulmonary resuscitation. New York: Springer-Verlag, 1977:132–7.
42. Greenberg MI, Roberts JR, Baskin SI, Wagner DK. The use of endotracheal medication for cardiac arrest. Topics Emerg Med 1979;1:29–40.
43. Chu SS, Rah KH, Brannan MD, Cohen JL. Plasma concentration of lidocaine after endotracheal spray. Anesth Analg 1975;54:438–41.
44. Mattar JA, Weil MH, Shubin H, Stein L. Cardiac arrest in the critically ill. II. Hyperosmolal states following cardiac arrest. Am J Med 1974;56:162–8.
45. Bishop RL, Weisfeldt ML. Sodium bicarbonate administration during cardiac arrest: effect on arterial pH, PCO_2, and osmolality. JAMA 1976;235:506–9.
46. Benowitz NL. Clinical applications of the pharmacokinetics of lidocaine. Cardiovasc Clin 1974;6:77–101.
47. Lieberman NA, Harris RA, Katz RI, Lipschutz HM, Dolgin M, Fisher VJ. The effects of lidocaine on the electrical and mechanical activity of the heart. Am J Cardiol 1968;22:375–80.
48. Wyman MG, Lalka D, Hammersmith L, Cannom DS, Goldreyer BN. Multiple bolus technique for lidocaine administration during the first hours of an acute myocardial infarction. Am J Cardiol 1978;41:313–17.
49. Wyman MG, Hammersmith L. Comprehensive treatment plan for the prevention of primary ventricular fibrillation in acute myocardial infarction. Am J Cardiol 1974;33:661–7.
50. Winkle RA, Glantz SA, Harrison DC. Pharmacologic therapy of ventricular arrhythmias. Am J Cardiol 1975;36:629–50.
51. Gilmore JP, Siegel JH. Mechanism of the myocardial effects of bretylium. Circ Res 1962;10:347–53.
52. Chatterjee K, Mandel WJ, Vyden JK, Parmley WW, Forrester JS. Cardiovascular effects of bretylium tosylate in acute myocardial infarction. JAMA 1973;223:757–60.
53. Bigger JT Jr, Jaffe CC. The effect of bretylium tosylate on the electrophysiologic properties of ventricular muscle and Purkinje fibers. Am J Cardiol 1971;27:88–92.
54. Holder DA, Sniderman AD, Fraser G, Fallen EL. Experience with bretylium tosylate by a hospital cardiac arrest team. Circulation 1977;55:541–4.
55. Todres ID, Rogers MC. Methods of external cardiac massage in the newborn infant. J Pediatr 1975;36:781–2.
56. Thales MM, Stobie GHC. An improved technic of external cardiac compression in infants and young children. N Engl J Med 1963;269:606–10.
57. Chameides L, Brown GE, Raye JR, Todres ID, Viles PH. Guidelines for defibrillation in infants and children. Report of the American Heart Association Target Activity Group: cardiopulmonary resuscitation in the young. Circulation 1977;56:502A–3A.
58. Gutgesell HP, Tacker WA, Geddes LA, Davis JS, Lie JT, McNamara DG. Energy dose for ventricular defibrillation of children. Pediatrics 1976;58:898–901.
59. Safar P, Bleyaert AL, Nemoto EM, Moossy J, Snyder JV. Resuscitation after global brain ischemia-anoxia. Crit Care Med 1978;6:215–27.
60. Safar P. Amelioration of postischemic brain damage with barbiturates. Curr Concepts Cerebrovasc Dis-Stroke 1980;15:1–5.
61. Safar P. Resuscitation of the arrested brain. In: Safar P, Elam JO, eds. Advances in cardiopulmonary resuscitation. New York: Springer-Verlag, 1977:177–81.
62. Caronna JJ, Finklestein S. Neurological syndromes after cardiac arrest. Stroke 1978;9:517–20.

63. Miller JR, Myers RE. Neuropathology of systemic circulatory arrest in adult monkeys. Neurology 1972;22:888–904.
64. Bleyaert AL, Sands PA, Safar P, et al. Augmentation of postischemic brain damage by severe intermittent hypertension. Crit Care Med 1980;8:41–7.
65. Cantu RC, Ames A, Dixon J, DiGiacinto G. Reversibility of experimental cerebrovascular obstruction induced by complete ischemia. J Neurosurg 1969;31:429–31.
66. Fischer EG, Ames A. Studies on mechanisms of impairment of cerebral circulation following ischemia: effect of hemodilution and perfusion pressure. Stroke 1972;3:538–42.
67. Safar P, Stezoski W, Nemoto EM. Amelioration of postischemic-anoxic brain damage by reflow promotion. In: Safar P, Elam JO, eds. Advances in cardiopulmonary resuscitation. New York: Springer-Verlag, 1977:182–6.
68. Goldstein A Jr, Wells BA, Keats AS. Increased tolerance to cerebral anoxia by pentobarbital. Arch Int Pharmacodyn Ther 1966;161:138–43.
69. Yatsu FM, Diamond I, Graziano C, Lindquist P. Experimental brain ischemia: protection from irreversible damage with a rapid-acting barbiturate (Methohexital). Stroke 1972;3:726–32.
70. Bleyaert AL, Nemoto EM, Safar P, et al. Thiopental amelioration of brain damage after global ischemia in monkeys. Anesthesiology 1978;49:390–8.
71. Snyder BD, Ramirez-Lassepas M, Sukhum P, Fryd D, Sung JH. Failure of thiopental to modify global anoxic injury. Stroke 1979;10:135–41.
72. Breivik H, Safar P, Sands P, et al. Clinical feasibility trials of barbiturate therapy after cardiac arrest. Crit Care Med 1978;6:228–44.
73. Bleyaert AL, Safar P, Nemoto E, Moossy J, Sassano J. Effect of postcirculatory-arrest life-support on neurological recovery in monkeys. Crit Care Med 1980;8:153–6.

Plasma Glucose Monitoring during Operation for Insulinoma

Analysis of experience with intraoperative plasma glucose monitoring during operation for insulinoma in 37 patients indicates that it provides an unreliable index of curative tumor excision. All but two of the patients had curative excision of insulinomas: by simple enucleation in 26 patients and by distal pancreatectomy in nine patients. Slope analysis was used to compare the rate of change in plasma glucose before and after tumor excision. In most patients, a progressive increase in plasma glucose was observed following induction of anesthesia and before tumor excision, even though glucose infusion was withheld. Two types of plasma glucose response were seen after curative tumor excision: (1) in 27 patients there was a typical "hyperglycemic rebound" with a significant further increase in plasma glucose slope within the first 30 minutes after curative tumor excision; (2) in eight patients there was no further increase in plasma glucose slope up to 90 minutes after tumor excision. All patients in the latter category eventually registered a hyperglycemic rebound, but it was delayed more than 90 minutes after tumor removal and long after the operation had been concluded. These delayed or "false-negative" responses in 23% of patients undergoing plasma glucose monitoring for insulinoma constitute a major limitation of the technique. It is evident that a lack of hyperglycemic rebound within 90 minutes after excision of an insulinoma should not be used as a criterion to proceed further with blind distal pancreatectomy. *(Tutt GO, Edis AJ, Service J, van Heerden JA: Plasma glucose monitoring during operation for insulinoma: a critical reappraisal. Surgery 1980;88: 351–6).*

CLINICAL reports

Retrolental Fibroplasia: A Multifactorial Disease

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Among the factors that are often thought responsible for the resurgence of cicatricial retrolental fibroplasia (RLF) in premature, low birth weight neonates, a history of oxygen therapy is often held to be of greatest importance (1-3). Indeed, a history of oxygen therapy is found in most low birth weight infants who develop the acute retinovascular changes; however, a history of oxygen therapy alone has little reliability in predicting those infants who develop the blinding cicatricial changes (4). These facts suggest that the development of RLF may be influenced by many factors that, although not always identified, may exert a summating effect on the premature retina. The following case report of a premature infant who developed blinding cicatricial RLF following an operation emphasized the importance of the multifactorial origin of this disease.

Case Report

A 1445-g infant was delivered vaginally at 31 weeks of gestation to a 24-year-old gravida 2, para 1 mother whose premature labor had been unsuccessfully treated for 3 days with intravenous ethanol. Assigned 1-minute and 5-minute Apgar scores of 9, the infant required neither oxygen nor resuscitation in the delivery room. On the 2nd day of life, the infant began to vomit bile-stained fluid. As a result, roentgenograms were obtained and these studies suggested that a mid-gut malrotation near the superior mesenteric artery was present. On the 7th day of life, without having an ophthalmologic evaluation, the unpremedicated infant was brought to the operating room for an exploratory celiotomy. After awake endotracheal intubation had been performed, anesthesia was induced and maintained with nitrous oxide (50% to 75%), halothane (0% to 1.5%), and oxygen (25% to 50%). During the 45-minute procedure, the F_{IO_2} (as monitored by an in-line oxygen analyzer) was 50% on three separate 5-minute periods; at all other times, F_{IO_2} varied between 25% to 30%. No operative or anesthetic complications occurred during the surgical repair of the obstruction. The child received humidified room air in the recovery room.

Postoperative recovery was marked by a persistent metabolic acidosis that required the intermittent administration of intravenous bicarbonate over an 11-day period, and by anemia that required transfusion of 15 ml of packed red blood cells on the 12th day of life. During this period the child also was found to have a patent, though asymptomatic, ductus arteriosus. The patient was discharged at 5 weeks of age and developed normally until 5 months of age when visual difficulties were suspected.

At 16 months of age, the child was referred to the pediatric ophthalmology clinic at our hospital because of decreased visual acuity. At that time, the response to hand motions was reduced in the right eye and was absent in the left eye; a retrolental mass in the left eye had resulted in early phthisis bulbi (a small shrunken globe); and in the right eye only a single small area of retina remained attached, and this area was under vitreous traction. The diagnosis of bilateral retinal detachments secondary to stage 5 cicatricial RLF was made.

At 19 months of age, the child underwent an unsuccessful attempt to repair the retinal detachment in the right eye by combined lensectomy-vitrectomy through a pars plana approach. Although the retina remained detached, the child did well until the 3rd postoperative week, when a total hyphema with secondary glaucoma was detected in the

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right eye. Therapy consisted of bed rest with sedation, carbonic anhydrase inhibitors, topical aqueous inflow inhibitors, and topical steroids. At the last follow-up visit, the 3¾-year old child appeared healthy, and ambulated well in familiar surroundings. Light perception was present in the right eye, although residual clotted blood persisted in the anterior chamber.

Discussion

The resurgence of RLF is not surprising in view of the increased survival rate of low birth weight infants who have received oxygen therapy (1–3). Approximately 45% of infants who weigh less than 1000 g at birth will develop acute retinal changes (4, 5). Of these infants who develop acute retinal changes, 80% to 90% will show spontaneous regression of these lesions (6) and when examined later in life, an unexplained myopia or temporal vitreal-retinal interface changes may be the only evidence of prior disease (7). However, the other 10% to 20% will develop cicatricial changes in the retina that can lead to severe visual impairment (6). This progression of the acute proliferative lesions to this severe form of the disease is unpredictable and most likely is influenced by factors other than perinatal oxygan exposure alone.

Although the degree of morphologic immaturity in the infant described was probably of greatest importance, a number of other perinatal factors most likely also contributed to the development of severe bilateral retrolental masses. Factors that may have had an effect on the development of our infant's disease include the following: (*a*) course of pregnancy and labor, (*b*) duration of pregnancy, (*c*) birth weight of the infant, (*d*) condition of the baby at birth, (*e*) course of the neonatal period of life, and (*f*) duration and amount of oxygen therapy.

Specifically, our experience in the neonatal intensive care nurseries at North Carolina Memorial Hospital (Table) agrees with that of other investigators who have shown that the degree of morphologic and functional immaturity of the premature infant are of great importance in determining the incidence of retinopathy (4–6, 8). The possible role of other factors in influencing the risk of RLF is less understood; however, in our patient we believe that factors other than gestational age and birth weight probably were also important in influencing the sensitivity of the retina. For example, the antenatal administration of ethanol to arrest premature labor could have been associated with the development of maternal acidosis (9, 10). Although the effects of ethanol on the fetal eye have not been studied, the development of fetal acidosis secondary to maternal acidosis would be expected to increase oxygen delivery to the retina (11). Similarly, in view of the histopathologic correlation recently described between RLF and patent ductus arteriosus in two cyanotic infants (12, 13), the possible relationship of patent ductus to RLF must be considered.

TABLE

Incidence of Retinopathy in Premature Infants of Different Birth Weights

	<1000 g		1000 to 1500 g		>1500 g	
	No. with retinopathy	No. examined	No. with retinopathy	No. examined	No. with retinopathy	No. examined
Flynn (4)	21	46	32	281	2	651
McCormick (8)†	41	83	85	393	18	751
Kingham (5)	28	—*	37	—	3	—
Flynn et al (6)†	56	90	106	468	11	303
Merritt et al (this study)	25	57	9	105	1	70

* —Total number in all weight categories is 384.
† Data from histograms.

Oxygen administration during general anesthesia, as in our patient, also has been suggested by Betts et al (14) as another factor that might predispose to the development of cicatricial RLF. In their report of heterozygous twins, baby A, a 1140-g girl, received oxygen on the 3rd day of life during and after surgery for duodenal atresia. The inspired oxygen administered to this twin was elevated for 275 minutes, and the radial Pa_{O_2} varied from 64 to 325 torr. During the 7th week of life, this twin was diagnosed as having active stage II retinopathy of prematurity which developed into cicatricial stage II RLF by the 7th month. Twin B, a 1440-g girl, developed normally with no evidence of retinal disease.

Although a number of similarities exist between our patient and the one described by Betts et al (14), a major noteworthy difference, which we believe could explain the greater severity of retinal disease in our patient, is the severity of the accompanying problems. The postoperative course in our patient was marked by the development of persistent acidosis and by anemia that required the transfusion of adult red blood cells. Both of these factors may have increased oxygen delivery to the retina; acidosis increases oxygen delivery by inducing a rightward shift in the oxygen dissociation curve (11), and the transfusion increases oxygen delivery by replacing the favorable dissociation curve of fetal hemoglobin with the rightward displaced dissociation curve of adult red cells

(15, 16). Thus, although oxygen was administered for a shorter intraoperative period and was not administered after surgery to our patient, we believe that these postoperative factors, in combination with the other previously discussed factors, rendered the retina of our patient susceptible.

In summary, the occurrence of blindness in the infant discussed herein reemphasizes the importance of considering the multifactorial nature of RLF during the care of premature infants. Prematurely born infants are at risk and remain at risk for RLF until their retinal vasculature completes its growth at approximately 36 to 40 weeks after conception. Because this postconceptional age is often difficult to determine, an ophthalmologic evaluation of the premature infant has been suggested as a way of determining retinal maturity. However, opacities in the ocular media of premature infants often preclude meaningful examination of the temporal retina which is often most susceptible to RLF. Therefore, an ophthalmologic evaluation may not be reliable in assessing the risk for RLF. If gestational age cannot be determined accurately, a birth weight *less than* 1500 g seems to be *the best indicator* of increased risk for RLF (17).

During the care of such an infant, an attempt should be made to limit factors that may have cumulative deleterious effects on the sensitive retina. In particular, because the initiating process of retinal vasoconstriction occurs more readily in the presence of hyperoxia, an attempt should be made to limit the retinal arterial oxygen tension at a level not higher than 80 to 90 torr. Direct measurement of oxygen tension in preductal arterial blood is most useful in this assessment; indirect assessment of oxygenation via the measurement of inspired or transcutaneous oxygen tension is also useful, but cannot totally supplant direct assessment.

REFERENCES

1. James LS, Lanman JT. History of oxygen therapy and retrolental fibroplasia. Pediatrics 1976;57:591–642.
2. Fitzhardinge PM. Follow-up studies on the low birth weight infant. Clin Perinatol 1976;3:503–16.
3. Pearce WG. Causes of blindness in children. Can J Ophthalmol 1975;10:469–72.
4. Flynn JT. Acute proliferative retolental fibroplasia: Evolution of the lesion. Albrecht Von Graefes Arch Klin Exp Ophthalmol 1975;195:101–11.
5. Kingham JD. Acute retrolental fibroplasia. Arch Ophthalmol 1977;95:39–47.
6. Flynn JT, Cassady, J, Essner D, Merritt JC, et al. Fluorescein angiography in retrolental fibroplasia: experience from 1969–1977. Ophthalmology 1979;86:1700–23.
7. Yamamoto M, Tatsugami H, Bun J. A follow-up study of refractive errors in premature infants. Jpn J Ophthalmol 1979;23:435–43.
8. McCormick AQ. Retinopathy of prematurity. Curr Probl Pediatr 1977;7:1–28.
9. Fuchs F, Fuchs AR, Poblete VF, et al. Effect of alcohol on threatened premature labor. Am J Obstet Gynecol 1967;99: 627–37.
10. Zlatnic FJ, Fuchs F. A controlled study of ethanol in threatened premature labor. Am J Obstet Gynecol 1972;112:610–2.
11. Shappell SD, Lenfant CJM. Adaptive, genetic and iatrogenic alterations of the oxyhemoglobin-dissociation curve. Anesthesiology 1972;37:127–39.
12. Kalina RE, Hodson WA, Morgan BC. Retrolental fibroplasia in a cyanotic infant. Pediatrics 1972;50:765–8.
13. Naiman J, Green WR, Patz A. Retrolental fibroplasia in hypoxic newborn. Am J Ophthalmol 1979;88:55–8.
14. Betts EK, Downes JJ, Schaffer DB, et al. Retrolental fibroplasia and oxygen administration during general anesthesia. Anesthesiology 1977;47:518–20.
15. Stern L. Oxygen toxicity in premature infants. Albrecht Von Graefes Arch Klin Exp Ophthalmol 1975;195:71–6.
16. Aranda JV, Clark TE, Maniello R, et al. Blood transfusion: possible potentiating risk factor in retrolental fibroplasia. Pediatr Res 1975;9:362.
17. Kinsey VE, Arnold HJ, Kalina RE, et al. PaO_2 levels and retrolental fibroplasia: A report of the cooperative study. Pediatrics 1977;60:655–68.

ANESTH ANALG
60:112-115, 1981

Intra-arterial Chloroprocaine for the Control of Pain Associated with Partial Splenic Embolization

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Transcatheter arterial embolization of the spleen has been used as an alternative to surgery in selected cases of hypersplenism (1, 2). This technique consists of percutaneous placement of a catheter into either the femoral or axillary artery and advancing its tip into the splenic artery. The embolic material used to embolize the spleen consists of particles of absorbable gelatin sponge (Gelfoam) suspended in an antibiotic solution. No attempt is made to embolize the entire spleen; instead, the procedure is terminated when approximately two thirds of the splenic parenchyma has been ablated by the embolization procedure.

A significant side effect of this procedure is pain which is located in the left hypochondrium and lower left rib cage. The pain begins when the spleen is embolized and can last for several days after the procedure. The purpose of this report is to present a patient in whom 2-chloroprocaine hydrochloride (3%) injected into the splenic artery during the embolization procedure was successfully used to control the pain. Its advantages over the previously described methods used to control the pain associated with splenic embolization are also considered.

Case Report

A 20-year-old, 50-kg man was admitted to the Transplant Service at the Childrens Hospital of Vanderbilt University 17 months after a three-antigen HLA-match cadaver renal transplant for the treatment of renal transplant rejection. Optimum doses of cyclophosphamide for immunosuppressive treatment could not be employed because of a white blood cell count (WBC) of 1,500/mm^3. Laboratory data during this admission were consistent with chronic renal failure and included: blood urea nitrogen 113 mg/100 ml, creatinine 4.9 mg/100 ml, WBC 2,200/mm^3, platelet 165,000/mm^3, hemoglobin 5.7 g%, and potassium 3.5 mEq/L; prothrombin time: patient-10 seconds, control-11 seconds, ratio: 0.9; and partial thromboplastin time: patient-36 seconds, control-28 seconds, ratio: 1.2. Bleeding time was prolonged (30 minutes) and was not corrected by daily dialysis. Transplant renogram showed marginal function. Splenomegaly was demonstrated on the ^{99m}Tc sulfur colloid liver spleen scan (Fig 1, top). Because hypersplenism was felt to be responsible for the leukopenia, a splenic embolization was successfully undertaken to ablate partially the splenic parenchyma as shown in Fig 1, bottom. The partial ablation corrected the leukopenia allowing increased doses of cyclophosphamide immunosuppressive therapy to be used in the management of the renal transplant rejection.

Methods and Materials

The embolization procedure began by premedication with diazepam, 10 mg orally, 1 hour before the procedure. Selective splenic arteriography and splenic infarction consisted of placing a 6-French end-hold cobra catheter percutaneously into the right femoral artery using aseptic technique. Before the introduction of the catheter, the skin and subcutaneous tissue of the right inguinal region were anesthetized with 10 ml of 1% lidocaine. Once the catheter was in position in the femoral artery, it was advanced under fluoroscopic control into the peripheral segment of the splenic artery past the orifices of the dorsal pancreatic and pancreatic magna arteries.

A preinfarction baseline, selective splenic arteriogram was obtained with 50 ml of iothalamate meglumine, 52%, and iothalamate sodium, 26% (Vascoray), contrast media. This demonstrated splenomegaly and the splenic vasculature (Fig 2, top). After this arteriogram and immediately before the embolization procedure, 180 mg of 2-chloroprocaine hydrochloride (3%) was injected through the catheter into the splenic vasculature. Approximately 20 minutes after this injection the spleen was infarcted using 1.5 ml of Gelfoam as the embolizing material. Before its use, the Gelfoam had been soaked for 3 hours in 100 ml of an antibiotic solution containing 500 mg of cefazolin (Ancef) and 80 mg of gentamicin. The total amount

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Received from the Departments of Anesthesiology, Radiology and Radiological Sciences, Pediatrics, and Veterans Administration Transplant Service, Vanderbilt University School of Medicine, Nashville, Tennessee. Accepted for publication October 27, 1980.

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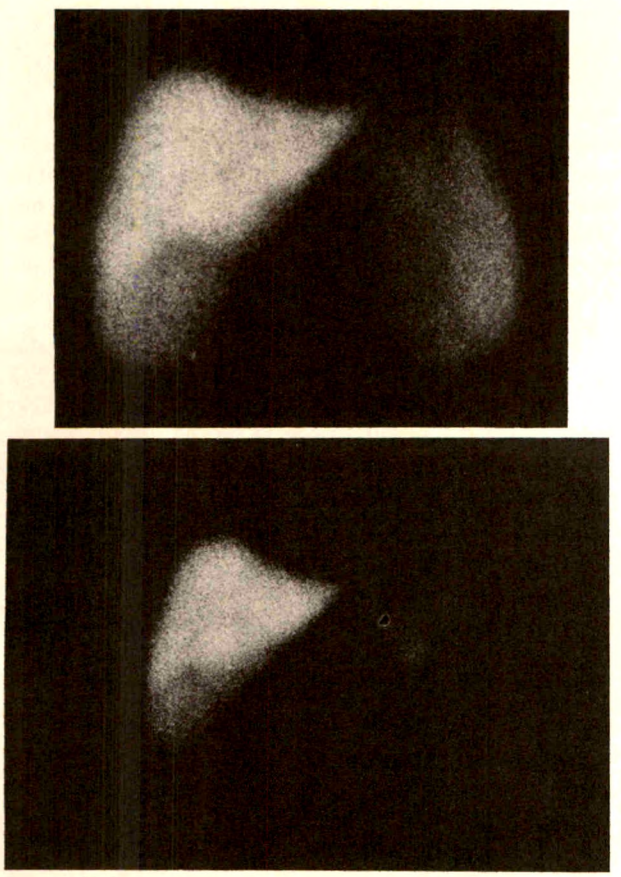


FIG 1. ^{99m}Tc liver spleen scan showing splenomegaly (top) and after embolization showing 80% infarction of splenic parenchyma (bottom).

of these antibiotics placed into the splenic vasculature during the embolization procedure was 90 mg of cefazolin (Ancef) and 15 mg of gentamicin.

No pain or discomfort was experienced by the patient either during the embolization procedure or immediately after it, and vital signs remained essentially unchanged. Once the embolization procedure was completed an additional 90 mg of 2-chloroprocaine was injected through the catheter into the splenic vasculature. A postinfarction selective splenic arteriogram (Fig 2, bottom) was then obtained with 20 ml of Vascoray contrast media to determine the extent of the splenic infarction. This showed that the main splenic arterial branches, to both the upper and lower poles of the spleen, had been occluded resulting in 80% infarction of the splenic parenchyma. The embolization procedure was then concluded as the desired degree of splenic infarction had been obtained.

The patient was taken to the pediatric intensive care unit and observed for 4 days. He continued to rest comfortably and did not complain of any pain or discomfort.

The patient's leukopenia improved dramatically and his cyclophosphamide was increased to 75 mg, at which point the rejection process declined (Figs 3 and 4). A ^{99m}Tc sulfur colloid liver spleen scan showed two thirds of the splenic parenchyma had been ablated (Fig 1, bottom). The patient was discharged from the hospital approximately 2 weeks after the partial splenic embolization and 8 weeks later was stable with serum creatinine levels of 2.6 mg/100 ml,

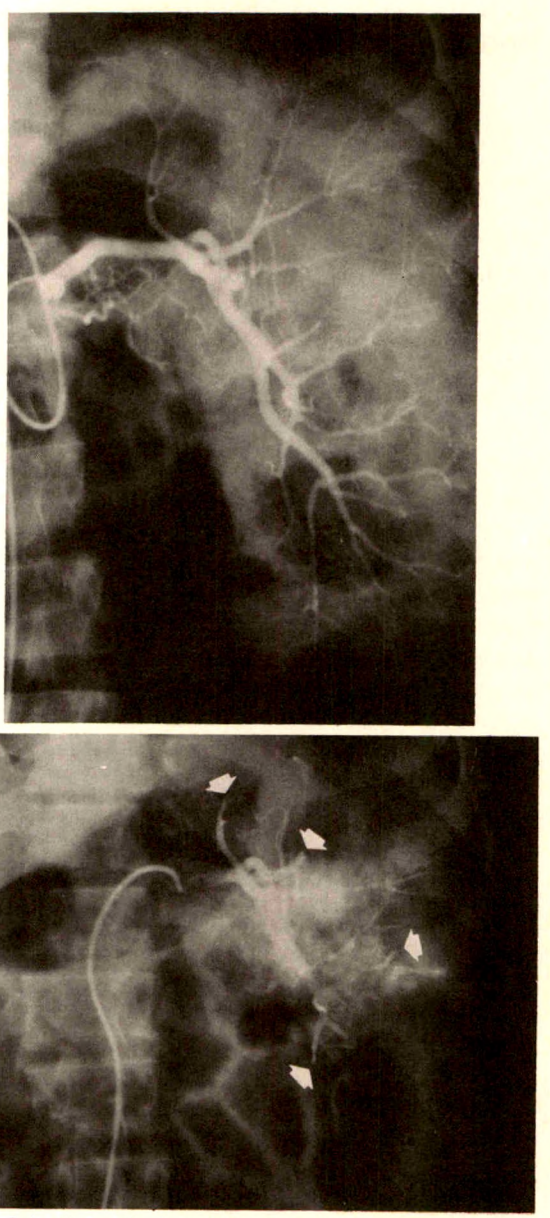


FIG 2. Selective splenic arteriogram showing splenomegaly (top) and postembolization arteriogram showing occlusion of multiple intrasplenic arteries (bottom, note arrows).

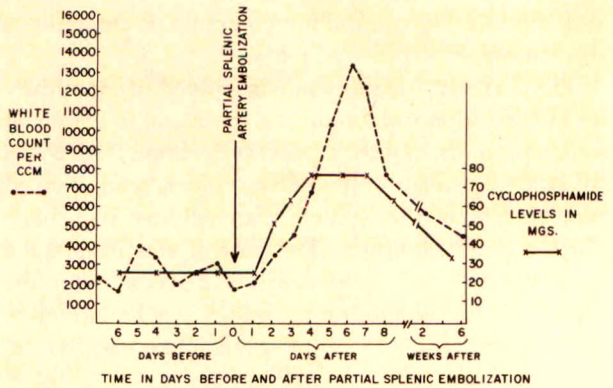


FIG 3. White blood cell counts correlated with cyclophosphamide oral dosages before and after partial splenic embolization.

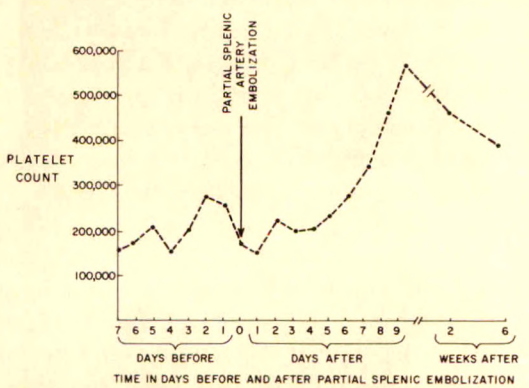


FIG 4. Platelet counts before and after partial splenic embolization.

and a WBC of 4,400/mm^3, and was taking 62.5 mg of cyclophosphamide daily. Repeated liver spleen scans over an 8-week period showed no change in the size of the spleen.

Discussion

The presence of hypersplenism, particularly leukopenia, restricts the use of cyclophosphamide and/or azathioprine for effective control of renal transplant rejection. Surgical splenectomy is relatively hazardous, not only because of the impaired wound healing in these patients, but also because of the resulting immunodeficiency that may follow. Rejection of the renal graft is a frequent complication. Consequently, partial splenic embolization is particularly attractive to nephrologists and physicians managing kidney transplant patients not only because it is a nonsurgical procedure, but because enough splenic tissue is left intact to provide for the necessary immunologic needs of the body (2).

The pain resulting from partial splenic embolization is often severe and long-lasting. This pain is not only due to ischemia and infarction of the splenic parenchyma, but also due to vasospasm of the arterial tree. The location of the pain is in the left hypochondrium and left lower rib cage: anteriorly, laterally, and posteriorly. A significant number of patients complain of severe pain referred to the left shoulder and radiating down the left arm. The pain can mimic angina pectoris, especially in middle-aged patients. The duration of the pain is approximately 3 days. Because of the pain associated with partial splenic embolization, the resultant splinting of the chest wall predisposes to basilar atelectasis, sputum retention, cough suppression, and pneumonitis. Respiratory complications, particularly in patients with hypersplenism and leukopenia, are a serious problem and, if not adequately managed, can lead to the rapid demise of the patient. For these reasons and for humane reasons, pain control is a major aspect of management of patients having partial splenic embolization during and after the procedure.

General anesthesia is possible, but not desirable, because of the high risk into which these patients are categorized, and general anesthesia cannot be continued for the 3 days when postembolization pain is severe.

Intravenous narcotics, e.g., meperidine (25 to 50 mg), have been used immediately before and after embolization. The deranged metabolism and elimination of most drugs, including narcotics, in patients with chronic renal failure is well known. The resultant accumulation of narcotics can produce respiratory depression with associated hypoxia and hypercarbia, which, if left untreated, may necessitate ventilatory support. Furthermore, the reduction in intravascular volume associated with chronic dialysis in chronic renal disease predisposes to sudden hypotensive episodes following intravenous narcotics.

The use of sedatives is also associated with problems. The minor tranquilizers used alone may worsen the pain because of their antianalgesic effects. The major tranquilizers such as droperidol can, in addition to making the pain worse, induce hypotension because of their alpha-blocking effects.

Spinal analgesia is probably contraindicated not only because of the hemodynamic sequelae, but also because of the inadequate level that can be safely acquired without compromising respiration. This is so because the changes occurring in the splenic parenchyma induce diaphragmatic irritation that would require blocking to a level of C-4 in order to provide satisfactory analgesia. In addition, because of the long duration of pain, a single dose spinal would be unsatisfactory.

D. G. Spigos, O. Jonasson, M. Mozes, and V. Capek (personal communication) treated one case with continuous epidural analgesia with 0.5% bupivacaine hydrochloride, which not only provided complete elimination of the pain during the embolization procedure but also during the postembolization period. The indwelling catheter was left in the epidural space for 72 hours. This technique appealed to us, but was not used in our case because of the persistent and prolonged bleeding time of 30 minutes.

Because of these objections and restrictions, we decided to use the local anesthetic 2-chloroprocaine hydrochloride by injecting it directly into the splenic artery immediately before injecting the embolic material. Chloroprocaine is an ester-linked local anesthetic that is rapidly hydrolyzed in the plasma by serum cholinesterase. It is relatively short acting and has a rapid onset of action. These pharmacologic considerations influenced our choice of chloroprocaine over the other local anesthetics and we accepted the fact that analgesia, if obtained, would be relatively brief.

As indicated in the case report, the patient experienced no pain or discomfort and there were no changes in pulse rate, ECG, or blood pressure. At the end of the embolization, we decided to augment the previously administered chloroprocaine by giving another dose (90 mg) intra-arterially before removing the catheter. This, too, proved effective; the patient had no significant pain or discomfort for the rest of his stay in the hospital.

It must be emphasized that all the usual precautions were taken so that rapid endotracheal intubation and resuscitation could be initiated at any time if necessary, and the patient's cardiovascular and respiratory status were monitored continuously. His premedication before the procedure was diazepam, 10 mg orally. Not only did this drug provide sedation but, because it increases the seizure threshold (this patient was epileptic), it may have provided some degree of prophylaxis against possible seizures.

Widrich et al (3), Gerlock et al (4), Gordon and Westcott (5), and Guthaner et al (6) have reported on the use of intra-arterial injection of local anesthetic before peripheral angiographic studies. This has been found to be safe and effective and has decreased the pain and burning associated with these procedures. In fact, many radiologists now routinely add lidocaine to their contrast medium before lower extremity angiography.

One of the striking features of this case was the prolonged analgesia obtained. Whereas we did not obtain preembolization serum cholinesterase levels, we did obtain a postembolization level and this was 1104 μU/ml—a very low level in our institution (normal values, 1875 to 3125 μU/ml). The chronic dialysis and the liver dysfunction could possibly account for the low value and this could possibly contribute to the prolonged action of the chloroprocaine. The speculated mechanism of action of chloroprocaine in this case is unclear. The vasodilatory effect of chloroprocaine on the splenic vasculature before the vasospasm induced by the embolic material is a possibility. It is interesting to note that upon injection of the second dose of chloroprocaine, there was a decrease in systolic blood pressure of 20 torr. This lasted for about 10 minutes and returned to previous levels without therapy.

In summary, we present a case of pain control following partial splenic embolization using intra-arterial chloroprocaine immediately before and after the injection of the embolic material. Severe pain, which usually accompanies this procedure and lasts for about 3 days, was completely absent in this patient. His leukopenia improved, his cyclophosphamide levels were increased, and his transplant rejection was reversed.

REFERENCES

1. Spigos DG, Jonasson O, Mozes M, Capek V. Partial splenic embolization in the treatment of hypersplenism. AJR 1979;132:777–82.
2. Witte CL, Ouitt TW, Van Wyck DB, Witte MH, O'Mara RE, Woolfenden JM. Ischemic therapy in thrombocytopenia from hypersplenism. Arch Surg 1976;111:1115–21.
3. Widrich WC, Singer RJ, Robbins AH. The use of intra-arterial lidocaine to control pain due to aorto-femoral arteriography. Radiology 1977;124:37–41.
4. Gerlock AJ, Duncan TR, Nickell CR. Intravenous lidocaine: an effective analgesic for lower extremity radiography. Radiology 1979;133:789–90.
5. Gordon IJ, Westcott JL. Intra-arterial lidocaine: an effective analgesic for peripheral angiography. Radiology 1977;124:43–5.
6. Guthaner DF, Silverman JF, Hayden WG, Wexler L. Intra-arterial analgesia in peripheral angiography. AJR 1977;128:737–9.

ANESTH ANALG
60:116-117, 1981

Modified Endotracheal Tube for Airway Management of Children with Facial Burns

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Respiratory care of the severely burned patient is always a problem, but is particularly difficult when the patient has sustained facial burns or has suffered perioral and nasal burns as a result of being burned in an enclosed space (1, 2).

The prime concern in caring for a burned patient is evaluation of the adequacy of the patient's airway. Edema of the head and neck, supraglottic, and glottic areas is the most common cause of airway obstruction (3, 4). Patients who are in significant respiratory distress on admission or whose airways might later be compromised by edema should be intubated immediately; if tracheal intubation is delayed severe swelling may make insertion of the tube impossible (1). Because it is associated with a higher incidence of tracheal and pulmonary complications than simple intubation, a tracheostomy should be done only when absolutely necessary to ensure an adequate airway (5).

Appropriate immobilization of the endotracheal tube following intubation is often difficult to accomplish. Adhesive tape or ties may not be suitable means of securing the tube since antimicrobial creams, often used in the management of facial burns, provide an unreliable base for adhesive tape and ties. We have found that placement of a modified, standard, thin-walled polyvinyl chloride endotracheal tube provides a safe means of controlling the airways of patients who have facial burns. The strength, elasticity, and nontoxic properties of polyvinyl chloride make it ideal for the manufacture of tracheal devices, and especially suitable for the modification of the endotracheal tube here described (6). In addition, the modified tube cannot possibly slip down the trachea should it become inadvertently disconnected from the adaptor.

The endotracheal tube should be of appropriate diameter and length to extend from the mouth or nostrils to the midtrachea, a distance that may be estimated from external landmarks, a chest radiograph, or available tables (7). It is preferable to overestimate slightly the length of the tube in order to avoid inserting a tube that is too short. The tube should then be marked with a water-resistant marker pen at the point where it will exit the mouth or nose. The nonbeveled end is slit down both sides to the mark to create a Y-shaped appliance. Once cut, the two flanges of the tube adopt a curled shape; thus it is the smooth, convex side that is always in contact with the burned areas, greatly minimizing possible further damage to tissues which might result from sharp edges. A small hole is cut in each of the split portion of the tube so that twill ties may be attached. The intubation with the intact portion of the tube is accomplished in the usual way and the split ends of the tube are then spread apart to act as flanges. These flanges are shaped to conform to the patient's face, and the tube is secured around the patient's neck by means of the twill ties at the end of each flange (Figure). Finally, a standard endotracheal tube adapter is connected to the tube where it was split. This

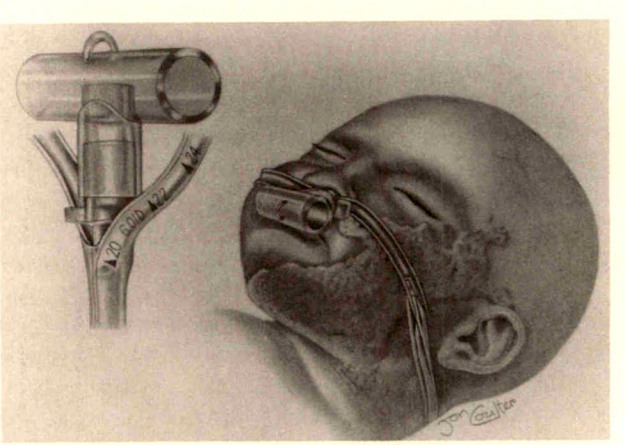


FIGURE. Modified endotracheal tube in place in child with facial burns. Tube has been secured with twill tape around the child's neck in a manner similar to that used to secure a tracheostomy tube. Note that flanges of the tube conform to curve of face. Twill tape can be loosened if tissue edema progresses. Inset depicts in more detail the split endotracheal tube with connector in place.

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Received from the Departments of Anesthesiology and Pediatrics, University of Pittsburgh, School of Medicine, Pittsburgh, Pennsylvania. Accepted for publication November 4, 1980.

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connector, the external diameter of which should be slightly larger than that of the internal diameter of the endotracheal tube, upon insertion stretches the opening of the tube slightly and results in a tight fit. This is a desirable feature since there is less chance of the adaptor becoming disconnected from the tube when ventilator tubings are attached. Following intubation, a chest radiograph may be obtained to verify that the tube has been properly positioned.

This tube has been used in six children whose ages ranged between 13 months and 7 years. The internal diameters of the tubes varied between 4.5 mm and 6.5 mm; duration of intubation varied from 9 days to 23 days, with a mean duration of 9 days. No cracking or splitting of the tube beyond the point to which it was split was observed, nor did the twill tapes stretch the holes in the flanges. There has been no significant degree of damage to the nose as a result of using this endotracheal tube adaptation.

Although experience with this modified endotracheal tube has been limited to children, this tube could also be adapted for use in adults.

REFERENCES

1. Barlett RH, Nicole M, Tavis MJ, Allyn PA, Furnas DW. Acute management of upper airway in facial burns and smoke inhalation. Arch Surg 1976;111:744–9.
2. Mellins RB, Park S. Respiratory complications of smoke inhalation. J Pediatr 1975;87:1–7.
3. Phillips AW, Cope O. Burn therapy. III. The revelation of respiratory tract damage as a principal killer of the burned patients. Ann Surg 1962;155:1–19.
4. Harrison HN. Respiratory tract injury, pathophysiology and response to therapy among burned patients. Ann NY Acad Sci 1968;150:627–38.
5. Stone HH, Martin JD. Pulmonary injury. associated with thermal burns. Surg Gynecol Obstet 1969;129:1242–6.
6. Lontz JF. Static and dynamic stress considerations in the design and use of polymeric materials in prosthetic applications. Ann NY Acad Sci 1968;146:166–92.
7. Smith RM. Anesthesia for infants and children. 4th ed. St. Louis: CV Mosby Co, 1980:175.

Respiratory Mechanics in Quadriplegia

Pulmonary mechanics and inspiratory muscle pressures were studied in relation to electromyograms (EMG) of the respiratory muscles in ten chronic quadriplegic patients. Transdiaphragmatic pressures at maximal inflation were normal, but minimal pleural pressures at functional residual capacity (FRC) were reduced to about half the normal values. On the basis of the parasternal intercostal EMG results, two groups were defined. In eight patients (group 1), no electomyographic activity was found in the intercostal muscles, even during large inspiratory maneuvers. In two patients (group 2), both intercostal and diaphragmatic activities were recorded during inspiration, and intercostal EMG activity increased with increasing inspiratory volume. Patients in group 1 had reduced FRC, transpulmonary pressure at FRC, and static expiratory compliance; therefore, the pressure-volume curves of the lungs resembled those obtained in patients with generalized weakness of the respiratory muscles. Specific compliance was normal in each patient, suggesting that the low compliance resulted in large part from the collapse of air spaces. Patients in group 2 had FRC, transpulmonary pressure at FRC, and lung compliance values within normal limits. The authors conclude that longstanding paralysis of intercostal muscles causes marked alterations in the elastic properties of the lungs and reduces the passive (outward) recoil of the chest wall. These findings suggest that the intercostal muscles normally stabilize the chest wall and prevent lung collapse. Moreover, intercostal surface EMG recordings may help to identify tetraplegic patients who may be at risk of developing respiratory failure during minor insults to the respiratory system. *(De Troyer A, Heilporn A: Respiratory mechanics in quadriplegia: the respiratory function of the intercostal muscles. Am Rev Respir Dis 1980;122:591–600).*

ANESTH ANALG
60:118-119, 1981

Intraoperative Dual-Mode Independent Lung Ventilation of a Patient with Bronchopleural Fistula

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This case describes an effective and safe method for the intraoperative anesthetic management of patients with bronchopleural fistula based upon dual-mode independent ventilation in which the healthy lung is ventilated by a conventional volume-set ventilator and the diseased lung (with bronchopleural fistula) by a high frequency jet ventilator.

Case Report

A 57-year-old man underwent a right upper lobectomy for bronchogenic carcinoma 5 months before present admission. After surgery, he developed empyema that subsequently resulted in development of a bronchopleurocutaneous fistula. Three months later he underwent drainage of his empyema and was discharged. He was admitted 2 months later having gained 17 pounds and without evidence of metastatic disease. There was no change in the fistula, which continued to drain. Thoracoplasty was decided upon as definitive therapy. The preoperative chest x-ray showed the previous right thoracotomy with elevation of the right hemidiaphragm. Arterial blood gas tensions were not measured before surgery.

The patient was premedicated with intravenous diazepam, 7.5 mg. After preoxygenation, anesthesia was induced with thiopental, 400 mg IV, with succinylcholine, 100 mg IV, for endotracheal intubation. A Carlens double-lumen endobronchial tube was inserted and both cuffs were inflated to ensure isolation of each lung. Anesthesia was maintained with 50% nitrous oxide in oxygen and intermittent doses of intravenous morphine (50 mg total), fentanyl (0.5 mg total), and pancuronium (10 mg). Before the patient was turned to the left lateral position controlled ventilation was instituted. The left lung was ventilated with a Ventimeter volume-set ventilator (Narco Air-Shields, Hatboro, PA) with a tidal volume of 500 ml at a rate of 9/min. The right lung, with the fistula, was connected to a VS 600 high frequency jet ventilator (Instrument Development Corp, Pittsburgh, PA) and ventilated at a rate of 150/min. Use of high frequency ventilation was approved by institutional Protection of Human Subjects Committee. Both ventilators delivered inspired oxygen concentrations of 50%. An arterial cannula was inserted for blood pressure monitoring and arterial blood sampling. The left lumen of the Carlens tube was connected to a MGA 1100 medical mass spectrometer (Perkin-Elmer, Pomona, CA) for continuous measurement of respiratory gases.

After induction of anesthesia, insertion of the Carlens tube, and start of independent lung ventilation, initial arterial blood gases in the supine position were: pH 7.45; Pa_{O_2}, 302 torr; Pa_{CO_2}, 33 torr; HCO_3^-, 23 meq/L; and BE, 0. With the patient in the left lateral position after the thoracoplasty was started the values were: pH, 7.46; Pa_{O_2}, 231 torr; pa_{CO_2}, 33 torr; HCO_3^-, 24 meq/L; and BE, +1. The procedure consisted of extrapleural resection of the second, third, and fourth ribs and lasted 2 hours 5 minutes. At its termination, two chest tubes were inserted. The patient's condition was stable throughout the procedure with no changes in ECG tracing, heart rate, or blood pressure. The peak bronchial pressures applied to the left and right lungs were 40 and 8 cm H_2O, respectively. The right lung was seen to expand well under the intact pleura. End-tidal carbon dioxide measured at the lumen connected to the volume-set ventilator remained at 4.5% during the procedure despite the presence of bronchopleural fistula. The mass spectrographic tracing of carbon dioxide concentrations from the right lumen, connected to high frequency ventilator, showed small fluctuations around mean expired

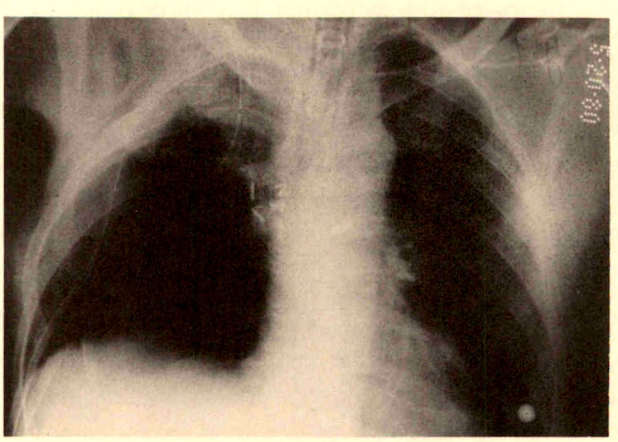


FIGURE. Chest x-ray film during high frequency ventilation immediately after thoracotomy. Endobronchial tube has its tip in left main stem bronchus in proper position. Pleural density is seen in right apex. Several upper posterior ribs have been resected. Both lungs are well expanded and free of infiltrate.

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Received from the Department of Anesthesiology, University of Pittsburgh, School of Medicine, Pittsburgh, Pennsylvania 15213. Accepted for publication November 10, 1980.
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values only (2.6% to 2.9%) and could not be used for end-tidal CO_2 measurements.

Following surgery a chest x-ray (Figure) obtained in the operating room showed both lungs to be well expanded. Dual-mode independent ventilation was continued for an additional 2 hours in the recovery room. Neostigmine (2.5 mg) and atropine (1.5 mg) were then given intravenously to reverse the effects of the pancuronium and the trachea was extubated. A repeat chest x-ray showed that both lungs remained well expanded, and the patient spent an uneventful night. The next morning arterial blood gas tensions with 10 L of O_2 administered through a face mask were: pH, 7.38; Pa_{O_2}, 135 torr; Pa_{CO_2}, 39 torr; HCO_3^-, 22 meq/L; and BE, −2. Drainage from the chest tubes decreased to 30 ml in 24 hours, at which time the tubes were removed. On his 3rd postoperative day, the patient developed partial atelectasis of the right middle and lower lobe, requiring fiberoptic bronchoscopy and removal of bronchial plugs. The patient was discharged on the 9th postoperative day.

Discussion

The endobronchial tube was originally designed by Carlens for bronchospirometry (1) before being introduced as a useful adjunct in anesthetic management of patients with unilateral lung infection (2). In the present case, the use of endobronchial anesthesia was necessary to prevent drainage of infected secretions into the healthy lung during the thoracoplasty. The requirement that the diseased right lung be isolated was compounded by the presence of right bronchopleural fistula. The large communication between the right upper lobe bronchus stump and the empyema cavity and cutaneous fistula presented a contraindication to conventional positive pressure ventilation. It could lead either to insufficient ventilation because most of the tidal volume would escape through the fistula, or might cause a tension pneumothorax. Independent ventilation of each lung was, therefore, desirable in order to deal with the different characteristics of each lung. High frequency ventilation has been demonstrated to achieve good gas exchange at low airway pressures and without hemodynamic impairment (3). Because of satisfactory previous experience with high frequency jet ventilation (4) and its use in the presence of a bronchopleural fistula (5), it was decided to ventilate the right lung with a high frequency jet ventilator. The difference in airway pressures was easily observed during ventilation with significantly lower peak pressures in the lung exposed to high frequency ventilation. The right lung could be seen to be well expanded throughout the procedure.

Differential independent lung ventilation is gaining increasing attention for management of patients with unilateral pulmonary pathology (6). This type of ventilation reduces the risk of damage to the healthy lung by avoiding high pressures that are required for proper ventilation of the diseased lung. One ventilator specially designed or two synchronized ventilators may be used for this approach (7). The method used by us, high frequency jet ventilation at a rate of 150/min for the diseased lung and a conventional volume-set ventilator for the other, demonstrated that synchronization is not required to obtain adequate ventilation. In addition, we were able to use the method best suited for handling the problem of a bronchopleural fistula. The patient remained hemodynamically stable, no demonstrable mediastinal shift was found, and satisfactory gas exchange was achieved.

In conclusion, greater flexibility in intraoperative management of patients with bronchopleural fistula can be achieved by the use of dual-mode independent lung ventilation, further extending the indications for high frequency jet ventilation.

REFERENCES

1. Carlens E. A new flexible double-lumen catheter for bronchospirometry. J Thorac Surg 1949;18:742.
2. Wylie WD. A practice of anaesthesia. Chicago:Year Book Medical Publishers, 1972.
3. Sjöstrand UH, Eriksson IA. High rates and low volumes in mechanical ventilation—not just a matter of ventilatory frequency. Anesth Analg 1980;59:567–76.
4. Klain M, Smith RB. High frequency percutaneous transtracheal jet ventilation. Crit Care Med 1977;5:280–7.
5. Carlon GE, Ray CR, Klain M, McCormack PM. High frequency positive pressure ventilation in management of a patient with bronchopleural fistula. Anesthesiology 1980;52:160–2.
6. Powner SD, Eross B, Grenvik A. Differential lung ventilation with PEEP in the treatment of unilateral pneumonia. Crit Care Med 1977;5:170.
7. Gallagher PJ, Banner MJ, Smith RA. A simplified method of independent lung ventilation. Crit Care Med 1980;8:396–9.

letters TO THE EDITOR

Rational Use of Reversal Agents

To the Editor:

Many recent articles, abstracts, and letters in the anesthesia literature have explored the use of doxapram, physostigmine, and naloxone to reverse the effects of inhalational anesthesia, narcotic-supplemented anesthesia, diazepam sedation, and ketamine. Advertisements in these same journals suggest "the sooner you start your patient on Narcan the sooner she'll be back following narcotic-supplemented anesthesia," and "more anesthesiologists are relying on Antilirium . . . ." Without denying the need for research in this area and without denying the appeal of being able to undo pharmacologically what has been done pharmacologically, I deplore the notion that recovery from anesthesia or sedation should automatically require the administration of a second drug to reverse its effects—an unfortunate extension, perhaps, of the necessity of reversing non-depolarizing muscle relaxants.

I suggest that a philosophy of reversal be based on the following tenets: (*a*) Anesthetics, narcotics, and sedatives should be chosen and administered so that the need to use a reversal agent does not arise; (*b*) Reversal agents are never absolutely necessary; (*c*) Reversal agents are drugs of convenience, and, as such, most serious complications associated with their use are avoidable; and, (*d*) Reversal agents may prolong recovery room stay because the duration of action of these agents may be shorter than that of the drugs they are given to reverse.

Although reversal agents have been safely administered to large numbers of patients, I agree with Andree (1) who said in a report of sudden death following naloxone administration, "most anesthesiologists have stopped thinking about the possibility of serious adverse reaction." Finally, rarely should more than 0.1 mg of naloxone per adult be used (2).

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REFERENCES

1. Andree RA. Sudden death following naloxone administration. Anesth Analg 1980;59: 782–4.
2. Purdell-Lewis JG. Studies of fentanyl-supplemented anaesthesia: effect of naloxone on circulation and respiration. Can Anaesth Soc J 1980;27:323–9.

Modified Laryngoscope for Endotracheal Intubation of Obese Patients

To the Editor:

The hazards of anesthesia in the obese patient are well known and are a concern to all anesthesiologists. Problems associated with obesity are both technical and pathophysiologic.

Because of the higher incidence of obstetric complications and the possibility of a larger volume of gastric contents, often with a low pH, obese parturients represent an especially high risk group. Laryngoscopy may, however, prove difficult in these patients because the chest and large breasts often impede the use of the usual laryngoscope handle. Recently, we devised a short handle specifically to circumvent the above mentioned problem (Figure). In five cases this handle gave adequate grip and leverage to perform laryngoscopy without any problem.



FIGURE. Differences in lengths of handles.

The short handle was fashioned by modifying a Penlite laryngoscope handle to accept a single 4.05-volt battery. First, the handle was cut flush with the positive end of the battery chamber; then a new one was constructed by using epoxy to glue the negative terminal into one end of a plastic tube cut from the barrel of a 20-ml syringe. This new handle was attached to the laryngoscope by slipping it over the stump of the old handle and drilling two holes that were tapped to accept a pair of small screws. Care was taken during the drilling to avoid cutting into the positive terminal. Finally, the electric circuit was closed by running a short wire inside the new handle from the negative terminal to the hook end of the laryngoscope. The entire conversion took less than 1 hour using hand tools and resulted in a strong, compact handle which provided a bright light. We think this new handle will

help to eliminate a common problem in laryngoscopy in obese patients.

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Malfunctioning Halothane Vaporizer

To the Editor:

Recently, Miller and Cascorbi (1) reported on a faulty OFF stop in a Cyprane Enfluratec vaporizer. We wish to report a similar malfunction in another Cyprane model, a Fluotec Mark III halothane vaporizer (Cyprane, Tonawanda, NY).

We had difficulty in maintaining depth of anesthesia with halothane in a cat following initial induction of anesthesia with intravenous methohexital. Little or no differential effect was seen in rotating the dial from OFF to the 5% position. Inspection of the vaporizer showed that the dial was rotated 180 degrees from normal. The vaporizer was removed from the system and anesthesia maintained with additional intravenous methohexital during the repair.

The dial of the vaporizer was removed. It was seen that the dial had been rotated 180 degrees past the OFF position. No obvious wear of the plastic guard ring in the cap was seen. It was theorized that a previous user may have turned the dial past the OFF position and overridden the detent in the plastic guard ring. The dial was rotated to the correct position, and the vaporizer reassembled and reinstalled in the anesthetic system. Depth of anesthesia was easily controlled by changing dial settings. Since this repair the vaporizer has been used for both induction and maintenance of anesthesia on numerous cats with no difficulty.

Our experience demonstrates two potential problems with the Fluotec Mark III: (*a*) overriding of OFF detent in plastic guard ring (1), and (*b*) leakage of halothane with dial set in OFF, or beyond OFF position (2).

We join with Miller and Cascorbi (1) in calling for proper preventative maintenance, but also suggest that the manufacturer consider replacing the plastic guard ring, which can flex and wear, with one fabricated of metal.

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REFERENCES

1. Miller JA, Cascorbi HF. Yet another vaporizer hazard. Anesth Analg 1980;59:805.
2. Cook TL, Eger EI II, Behl RS. Is your vaporizer off? Anesth Analg 1977;56:793–800.

A Simple Technique to Stop Hiccups during Endotracheal Anesthesia

To the Editor:

Hiccups are not uncommon in patients during general anesthesia. Although noted more frequently during upper abdominal, thoracic, and head and neck operations, hiccups can also occur during minor operations on other parts of the body. Intermittent spasm of the diaphragm disturbs the surgical field and prevents the surgeon from accomplishing delicate repair work. It annoys the surgeon and the anesthesiologist as there is no quick and effective way to stop the hiccups. The etiology of the hiccups is unknown. Several empirical treatments including positive pressure inflation of the lungs (1), catheter stimulation of the nasopharynx (2), nasopharyngeal instillation of ether (3), parenteral administration of methylphenidate (4), ketamine (5), edrophonium, ephedrine, doxapram, and muscle relaxants have all been used with varying amounts of success. In our experience, instillation of ether into the nasopharynx through a catheter has been the most effective method of suppression of hiccups. Because of possible danger of explosion with the widespread use of electric cautery, ether is, usually unavailable in most operating rooms. Since it has been hypothesized that the rapid cooling that occurs from evaporation of ether may result in suppression of hiccups, we thought cold water might be equally effective.

In 10 patients receiving endotracheal anesthesia complicated by intraoperative onset of hiccups, we instilled 5 ml of ice-cold (melted ice) water through one of the nostrils. In nine patients, the hiccups stopped immediately. One patient required instillation of another 5 ml of ice-cold water through the other nostril for suppression of the hiccups. We have been impressed with the good results obtained with this very simple technique. As yet, we have not had an opportunity to evaluate the effectiveness of this technique in awake patients or in patients with chronic hiccups. We certainly do not advocate a trial of this technique in an unconscious patient without endotracheal tube or in an awake patient with depression of cough reflex.

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REFERENCES

1. Baraka A. Inhibition of hiccup by pulmonary inflation. Anesthesiology 1970;32:271–3.
2. Salem M. An effective method for the treatment of hiccups during anesthesia. Anesthesiology 1967;28:463–4
3. Moses JA, Ramachandran KP, Surendran D. Treatment of hiccups with instillation of ether into nasal cavity. Anesth Analg 1970;49:367–8.
4. Gregory GA, Way WL. Methylphenidate in the treatment of hiccups during anesthesia. Anesthesiology 1969;31:89–90.
5. Shantha TR. Ketamine for the treatment of hiccups during and following anesthesia: a preliminary report. Anesth Analg 1973;52:822–4.

Faulty Y-Piece

To the Editor:

Many anesthesia circle systems incorporate a Y-piece with designated male and female terminals. These Y-pieces have two 22-mm male terminals that insert into the inspiratory and expiratory tubing on one end and one 15-mm female terminal that accepts the mask or endotracheal tube on the other. One such Y-piece is the Ryton inhaler Y (stock no 219-4534-700, Ohio Medical Products, Madi-

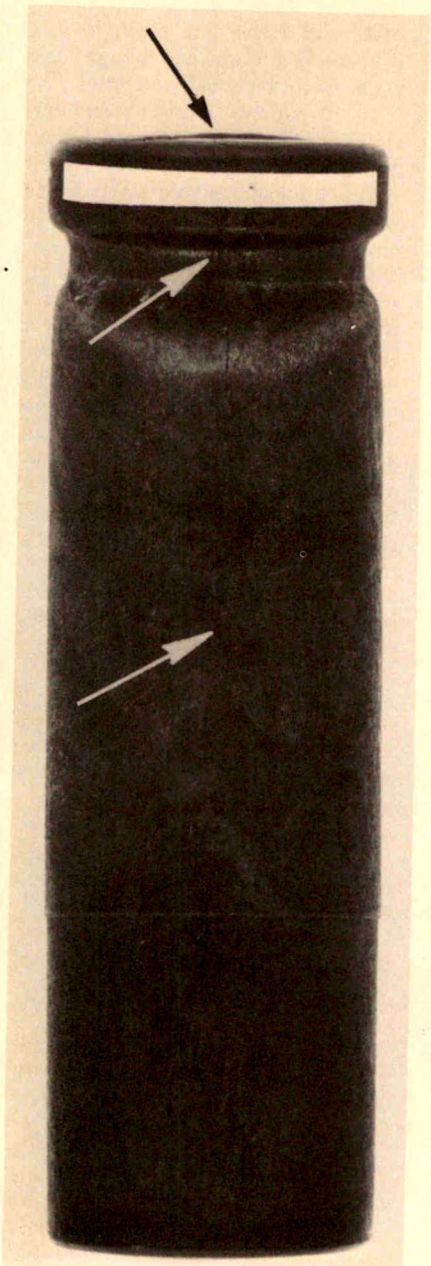


FIG 1. Ryton inhaler Y without Foregger elbow adapter inserted. Crack in molding seam appears minimal; white tape has been applied to help demonstrate crack.

son, WI). Composed of polyphenylene sulfide 70%, glass 15%, and carbon fiber 15%, this Y-piece has the typical two male 22-mm terminals on the proximal end that fit into the circle system tubing and a female 15-mm terminal that receives a 90-degree elbow adapter distally. Advantages include its light weight and elimination of potential chrome flaking which sometimes occurs on older metal varieties.

Recently there were serious leaks in our anesthesia circle system while using this inhaler Y. Inspection of the unconnected unit revealed a minimal crack in the molding seam (Fig 1). With insertion of a Foregger (15 mm) mask elbow adapter, a serious leak (Fig 2) occurred. To date, this has appeared in three of 10 units. These units are approximately 2 months old. Cleaning consists of brushing with soap and water followed by soaking in glutaraldehyde (Cidex).

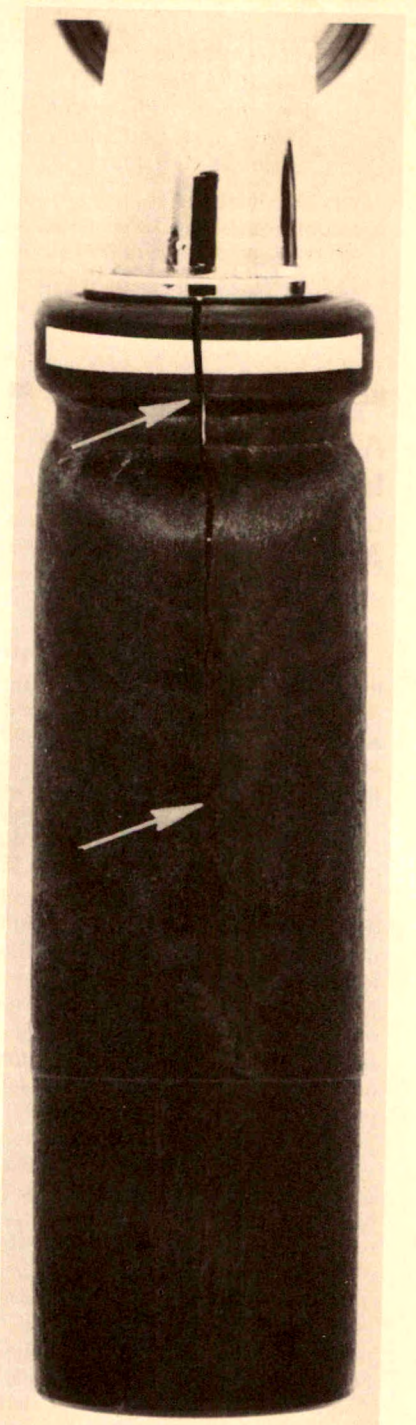


FIG 2. Ryton inhaler Y with Foregger elbow adapter inserted. Crack in molding seam has markedly increased.

The above problem was discussed with both the local Ohio Medical representative and the manager of product safety. As a result, testing was performed on the Y-piece (although a Foregger connector was not available). The tests indicated that the pressures required to cause a crack in the Y-piece ranged from 20 to 70 pounds, but that because of the large variation in force needed to split the Y-piece there was a possibility that some parts could split with lower pressures. The manufacturer also stated that this represented the only complaint received concerning splitting of the Y-pieces.

Consequently, we recommend that either all lightweight Ryton Inhaler Y-pieces or all Foregger 90-degree connectors be removed from equipment inventories where both are used. We further recommend that others using similar equipment do the same.

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Epidural Blood Patch

To the Editor:

The report by Reynolds et al (1) on spinal epiarachnoid hematoma as a complication of a rather unusual epidural blood patch (EBP) technique certainly emphasizes that intentionally entering the subarachnoid space and then withdrawing the needle into the epidural space is hardly a logical approach to management of post-spinal headache associated with a spinal tap. If the initial spinal tap results in a headache, a second dural puncture with a 22-gauge needle as part of EBP to treat the headache can hardly be expected to improve matters as a spinal tap with a 22-gauge needle is itself associated with a 9% incidence of spinal headaches (2). Six

EBPs in the same patient because of poor communication between three services in two hospitals, a record far exceeding the three EBPs reported in one patient by Di Giovanni and Dunbar (3), emphasizes yet again the necessity for close and effective communication between anesthesiologists and other physicians in the care of their patient.

The case report of Reynolds et al (1), serves also to remind us that EBP need not be the first choice in management of postspinal headaches. Bed rest, analgesics, oral or intravenous hydration, and intermittent injection or even continuous infusion of epidural saline remain the first choices; EBP is a second choice (4, 5). The case report further emphasizes that use of the "hanging drop" technique is not the most reliable nor the safest means for identification of the epidural space (5).

It is true that, as Reynolds et al (1) note, the question of "how many properly performed EBPs should be performed for persistent postlumbar puncture headaches is unresolved," but surely the answer is not *six* EBPs or "as many as needed." As Abouleish (6) points out, only 8% of patients with spinal headache need a second EBP; the overall success rate is 96.5%. Performing six EBPs in an attempt to achieve a 100% success rate, the use of such a novel technique that involves dural puncture with a 22-gauge needle, or the use of the hanging drop test for identification of the epidural space, may all be open to question.

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REFERENCES

1. Reynolds AF Jr, Hameroff SR, Blitt CD, Roberts WL. Spinal subdural epiarachnoid hematoma: a complication of a novel epidural blood patch technique. Anesth Analg 1980;59:702–3.
2. Vandam LD. Spinal anesthesia. In: Hall DE, ed. Anesthesiology. 2nd ed. Philadelphia: FA Davis Co, 1963:538.
3. Di Giovanni AJ, Dunbar BS. Epidural injections of autologous blood for postlumbar puncture headache. Anesth Analg 1970;49: 268–71.
4. Smith BE. Prophylaxis of epidural "wet tap" headache. Anesthesiology 1979;51:S304.
5. Bromage PR. Epidural analgesia. Philadelphia: WB Saunders, 1978:661, 183.
6. Abouleish E. Epidural blood patch for the treatment of chronic postlumbar puncture cephalgia. Anesthesiology 1978;49:291–2.

Epidural Narcotics

To the Editor:

It was a pleasure to read of a useful and well conducted trial of epidural narcotics for postoperative analgesia; one expects nothing less from Bromage and colleagues (1). Nevertheless I would welcome clarification of three points:

1. Was the dose of epidural methadone 1 mg as stated in the abstract or 5 mg (perhaps more likely) as in the text?

2. The authors state that the epidural dose of narcotic was diluted to between 8 and 20 ml depending on the operative site and the age of the patient. Did then the younger patients, who would from Dr. Bromage's classic earlier work require larger volumes, receive the more dilute epidural narcotic?

3. If epidural narcotics exert their effects after diffusion into the cerebrospinal fluid (CSF), how then can a segmental distribution of effect be produced similar to that of local anesthetics acting on the roots at the site of injection? The CSF lying beneath the site of administration in lumbar epidural blockade bathes the cauda equina. In my experience of pain blockade following lumbar epidural narcotics, the sacral segments are frequently spared. Such would not be the case if the effect was produced after diffusion into CSF.

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REFERENCE

1. Bromage PR, Camporesi E, Chestnut D. Epidural narcotics for postoperative analgesia. Anesth Analg 1980;59:473–80.

To the Editor:

We thank Dr. Reynolds for her comments. Dr. Reynolds is quite correct in pointing out a proofreading error in our abstract. Line 6 of the abstract (1) should have read methadone, 5 mg, instead of methadone, 1 mg.

Dr. Reynolds raises the question of possible inconsistencies in our data arising from variations in concentration of epidural narcotics. This possibility must be viewed in the context of our intent and our protocol. We set out to achieve two clinical objectives: (*a*) subjective relief of pain, and (*b*) maximal restoration of respiratory function (as measured by FEV_1) after upper abdominal surgery. To achieve these goals we made two assumptions: (*a*) dose requirements are likely to vary unpredictably from patient to patient, and therefore epidural narcotics should be administered incrementally until the goal of pain relief and a plateau of optimal FEV_1 had been reached; and (*b*) preliminary experiments in volunteers had indicated that the segmental level of a given dose of epidural narcotic was almost identical with the segmental spread of the same volume of local anesthetic (2). This finding seemed consistent with the rather similar ranges of molecular size, pK, and lipid solubility of the two classes of drugs. Therefore, we thought that of the three variables, i.e., dose, volume, and concentration, the first two would be more important in determining intensity and spread of analgesia than concentration. Accordingly, the dose of epidural narcotic was determined by individual patient requirements, whereas volume was determined by prior injection of local anesthetic and observation of adequate segmental spread both upward and downward. Concentration of narcotic varied inversely with volume and did not seem to be related to analgesic performance. The main determinants of volume of narcotic diluent in this series were the site of injection and, to a lesser degree, age and obesity. Midthoracic injections varied between 8 to 12 ml and lumbar injections between 12 to 20 ml.

Finally, Dr. Reynolds questions analogies between the kinetics of intraspinal local anesthetics and intraspinal narcotics, and she finds frequent "sacral sparing" after lumbar epidural injection. This is not surprising if *small* doses of narcotics are used, for precisely the same thing is seen with small doses of local anesthetic injected into the upper or midlumbar region of the epidural space. The ki-

netics of both classes of drug are rather similar, and both have been shown to diffuse from the cerebrospinal fluid into the surface of the neuraxis (3–5). The targets are different—mainly axonal for local anesthetics and mainly synaptic for narcotics, but the paths to the targets appear to be similar. Unlike Dr. Reynolds, we have not experienced sacral sparing in our lumbar narcotic injections; perhaps the difference lies in the regimens chosen. Our doses are not fixed but are given "quantum sufficiat" by injecting increments at appropriate intervals until the patient is comfortable. Dr. Reynolds administers a fixed dose in a small volume of 4 ml (F. Reynolds, personal communication, 1980). We would suggest that cases of "sacral escape" are merely reflections of insufficient dosage.

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REFERENCES

1. Bromage PR, Camporesi EM, Chestnut D. Epidural narcotics for postoperative analgesia. Anesth Analg 1980;59:473–80.
2. Bromage PR, Camporesi EM, Leslie J: Epidural narcotics in volunteers: sensitivity to pain and carbon dioxide. Pain 1980;9:145–60.
3. Bromage PR, Joyal AC, Binney JC: Local anesthetic drugs: penetration from the spinal extradural space into the neuraxis. Science 1963;140:392–4.
4. Cohen EN: Distribution of local anesthetic agents in the neuraxis of the dog. Anesthesiology 1968;29:1002–5.
5. Teschemacher HJ, Schubert P, Herz A: Autoradiographic studies concerning the supraspinal site of the antinociceptive action of morphine when inhibiting the hindleg flexor reflex in rabbits. Neuropharmacol. 1973;12:123–31.

Comparison of Digoxin and Dobutamine in Cardiac Failure

The hemodynamic effects of dobutamine were compared with those of digoxin in six patients with cardiac failure within 24 hours of onset of acute myocardial infarction. Dobutamine (8.5 μg/kg of body weight per minute) was given intravenously for 30 minutes and then discontinued until hemodynamics returned toward base line. Digoxin (12.5 μg/kg) was then given intravenously, and hemodynamics were recorded for 90 minutes. Dobutamine decreased left ventricular filling pressure (from 22.3 to 9.8 mm Hg, $p < 0.02$) and systemic vascular resistance (1686 ± 188 to 1259 ± 108 dynes·sec·cm^{-5}), and increased cardiac index (from 2.4 to 3.2 L/min/m^2 of body surface area, $p < 0.005$) and stroke work index (from 24.6 to 36.6 gm/m^2, $p < 0.02$), without changing heart rate or arterial pressure. In contrast, digoxin had no effect on filling pressure (18.3 vs 17.0) and only a slight effect on cardiac index (2.2 vs 2.4, $p < 0.05$) and stroke work index (21.9 vs 27.6, $p < 0.05$). Thus, dobutamine markedly increased cardiac output, decreased filling pressure, and relieved pulmonary congestion. Digoxin did not affect preload or afterload. *(Goldstein RA, Passamani ER, Roberts R: A comparison of digoxin and dobutamine in cardiac failure in patients with acute infarction and cardiac failure. N Engl J Med 1980;303:846–50).*

book REVIEWS

Functional Toxicity of Anesthesia, by D. L. Bruce, New York, Grune & Stratton, Inc., 1980, 125 pp, $15.50.

This monograph is one in a series titled *The Scientific Basis of Anesthesia*. Its objective is to keep the practicing clinician informed on important current topics in anesthesia. Although specifically aimed at the practicing anesthesiologist, this book is also suitable for nurse anesthetists and students.

The author's definition of functional toxicity, "anesthetic effects we'd rather not have," is intended to include the toxic effects of anesthetics that are temporary and reversible, as well as those that are irreversible. Reinforced repeatedly is the overall premise that patients are not "put to sleep" in a normal physiologic sense when they are anesthetized; rather, potent toxins having diverse effects on body functions are administered to induce an abnormal state. Thus, the author emphasizes the need for anesthesiologists to recognize how these agents affect the total patient, both acutely and over a longer period.

The book is organized into discussions of important organ systems, with a final chapter having a more encompassing heading of cell division. The first section of each chapter describes, in broad terms, the normal physiologic function of the particular organ system. Anesthetic-induced alteration of normal function is then presented with a discussion of each agent individually. Intravenous as well as inhalation anesthetics are included, with perhaps too much emphasis on the paleoanesthetics in view of the minimal modern day use of cyclopropane, diethyl ether, and chloroform. The succinct format necessitates a superficial description of normal physiology which the discriminating reader will find inadequate for real understanding of normal physiologic processes.

Some important topics, deserving extensive coverage in a monograph discussing toxicity of anesthetics, have been omitted or slighted. There is no mention of skeletal muscle toxicity, despite the death of more patients from malignant hyperpyrexia than from many other derangements that are included in the monograph. There are inadequate discussions of anesthesia and the fetus, and enflurane and seizure disorders. Isoflurane has been included in each chapter, but its importance appears minimized. This is unfortunate as both isoflurane and this monograph have been released in the same month. In fact, the putative carcinogenicity of isoflurane is mentioned briefly in only two sentences, despite the tremendous controversy regarding this issue during the past 5 years.

In spite of these shortcomings, the text is well organized, compact, and clear. The fluent, concise style allows one to read the entire book comfortably in less time than it takes to watch the Super Bowl. The author has made several significant contributions to anesthesia literature. First is his viewpoint that anesthesia is an iatrogenic illness and not just sleep, although many may disagree with this basic hypothesis.

Second, the book serves as a warning that anesthetics are not benign; a fact that is rarely appreciated by those outside our specialty. The author concludes that there are lessons to be learned by the surgeon, nurse, physician, patient, and attorney. All can only benefit from a better understanding of potential anesthetic toxicity. Last, although all of the scientific information is available in scattered sources elsewhere, the book brings together all of this data in one convenient text. If only for this reason, this monograph belongs in the libraries of anesthesia training programs and is recommended for those involved in the administration of anesthesia.

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Newborn Respiratory Care, by M. D. Lough, T. J. Williams, and J. E. Rawson, Chicago, Year Book Medical Publishers, Inc., 1979, 350 pp, $20.00.

This text, which includes 12 chapters written by 13 contributors, places great emphasis on the clinical respiratory care of the newborn. The first chapter provides valuable information on the development of the cardiorespiratory system; it contains 23 figures and four tables. The second chapter outlines resuscitation of the newborn. Abnormal respiratory conditions and radiologic findings in respiratory disease are reviewed in the following chapters. Separate chapters are dedicated to neonatal pharmacology and transportation of the high risk patient.

In the section on newborn respiratory care procedures, the technical aspects of thermoregulation, oxygen therapy, external cardiac massage, intubation, arterial cannulation, monitoring, and chest physiotherapy are detailed. The chapter on nursing care covers procedures including thermoregulation, feeding, and monitoring, as well as nursing responsibilities.

The chapters on continuous positive airway pressure and mechanical ventilation discuss theories, basic concepts, indications, methods of administration, and descriptions of the commercial systems available. The last chapter deals with the psychologic problems associated with having an ill infant. This book contains valuable information for all health professionals involved in the care of the newborn. The practical aspects make it useful for respiratory therapists, nurses, and physicians. Some sections may be more useful to one group of professionals than others. The material in this book would be helpful for anesthesiologists preparing for their specialty board examination.

Noticeable deficiencies include considerable overlapping by the contributors in certain areas and inconsistency of listing references. In addition, throughout the text some diagrams lack clarity. However, these criticisms are minor and should not detract from the merits of this book.

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Neuroanesthesia: Current Topics in Anaesthesia, Volume 3, by M. Marshall, Chicago, Year Book Medical Publishers, Inc., 1979, 78 pp, $18.95.

This book attempts to survey current neurosurgical anesthesia and intensive care practice in a concise manner. The author's goal is a difficult and noble one, but he is unsuccessful at accomplishing it.

The text draws upon the author's personal experience and interpretation of current neurosurgical knowledge. Many subjects important to a neuroanesthesiologist are only briefly mentioned, and the book is deficient in that it excludes discussing anesthetic procedures particular to arteriovenous malformations, transphenoidal hypophysectomy, chronic spinal cord injury, carotid endarterectomy, or extracranial-intracranial anastomosis.

The text is lightly illustrated and references are few. The book uses generic names that are commonly used in the United Kingdom, but there is a glossary of drugs used in other countries. The initial chapters are devoted to intracranial pressure, cerebral blood flow and metabolism, the effects of anesthetic techniques on these parameters, and monitoring of the neurosurgical patient. The following chapters discuss problems peculiar to the management of the patient with head injury, posterior fossa trauma surgery, and aneurysm surgery. The final chapters present the problems associated with anesthesia for neuroradiologic procedures and discuss neurosurgical emergencies.

In conclusion, this book provides a too brief survey of this expanding subspecialty of anesthesia that could better be provided by recent review articles on neuroanesthesia and intracranial hypertension. Other recently published books on neurosurgical anesthesia will provide both practitioners and residents a more thorough understanding of the subject.

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International Anesthesiology Clinics: Anesthetic Side Effects and Complications: Seeking, Finding, and Treating, edited by W. D. Owens, Boston, Little, Brown & Co., Fall 1980, 205 pp, $40/year.

How much of the subject, anesthetic side effects and complications, can one cover in 196 relatively small pages? For this, indeed, is the purpose of editor, William D. Owens, when he states "This issue of *International Anesthesiology Clinics* will not enlarge the overall data base (relating adverse outcomes to anesthesia) but it is intended to provide the reader with some guidance that will help reduce anesthetic side effects and complications."

Beginning with an overview of the subject and the problem of data collection, there follow 11 chapters, each devoted to one particular aspect of complications. Thus, there are sections on side effects and complications from drug therapy (preoperative, neuromuscular blockers), from effects of anesthesia on organ system function (respiratory, cardiovascular, nervous, renal, endocrine, hematologic, and immunologic), and complications related to monitoring and recovery room care. A final chapter discusses decision analysis—"an improved method of using data as it becomes available in the future."

One problem with a wide ranging topic in a smallish book is that, perforce, coverage may be superficial and incomplete. A few chapters, e.g., monitoring, preoperative drug therapy, suffer from this malady; they can do little more than scratch the surface. Many of the others, however, are tightly constructed, well conceived gems; these 15- to 20-page reviews cover the topic to a surprising depth and provide a useful, timely bibliography.

I believe that this book is a successful one. The information is of recent origin and concisely presented, and the price is reasonable. This book is recommended for students, practitioners, and libaries alike.

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BOOK NOTE

Basic and Clinical Sciences in Anesthesiology, Ninth Edition, by A. B. Tarrow and J. C. Erickson, Cedar Falls, IA, The Lydette Publishing Co., 1980, 563 pp, $23.25.

The ninth edition of this book continues to provide a source for review

of anesthesia. Almost 2,000 multiple-choice questions cover a wide range of topics of interest to the practicing anesthesiologist and to the trainee approaching the qualifying examinations. The learning experience gained from the use of this book is enhanced by the provision of succinct explanations, appropriate references to the medical literature, and an extensive index.

BOOKS RECEIVED

A Guide to Paediatric Anaesthesia, by J. M. Beasley and S.E.F. Jones, Boston, Blackwell Scientific Publications, 1980, 167 pp, $16.25.

The Practice of Electrocardiography, by T. M. Blake, Garden City, NY, Medical Examination Publishing Co, Inc, 1980, 236 pp, $12.00

Anesthesia and the Patient with Endocrine Disease, by B. R. Brown, Philadelphia, F. A. Davis Co, 1980, 203 pp, $24.00

Functional Toxicity of Anesthesia, by D. L. Bruce, New York, Grune & Stratton, Inc, 1980, 125 pp, $15.50.

A Practical Guide to Pediatric Intensive Care, edited by D. L. Levin, F. C. Morriss, and G. C. Moore, St. Louis, The C. V. Mosby Co, 1979, 499 pp, $24.50.

Physiology and Pharmacology of the Airways, edited by J. A. Nadel. New York, Marcel Dekker, Inc, 1980, 357 pp, $44.50.

Practical Points in Anesthesiology, Second Edition, by D. C. Stark, Garden City, NY, Medical Examination Publishing Co, Inc, 1980, 364 pp, $14.50.

To Make the Patient Ready for Anesthesia: Medical Care of the Surgical Patient, edited by L. D. Vandam, Menlo Park, CA, Addison-Wesley Publishing Co, Inc, 1980, 245 pp, $24.95.

Predicting Loss of Lung Function following Lobectomy and Pneumonectomy

Quantitative xenon 133 ventilation and technetium 99m macroaggregated albumin perfusion scans were performed in 85 patients with lung cancer who had resection of their tumor. The contribution of the lung to be resected to the overall pulmonary function and, therefore, the expected reduction in postoperative pulmonary function was calculated by combining the results of spirometry with the quantitative measurement of differential perfusion and/or ventilation according to several equations. This was done in an effort to determine the best method of predicting postoperative pulmonary function. The predicted postoperative forced expiratory volumes in the first second (FEV_1) from each of these calculations were compared to the observed postoperative FEV_1 in 37 patients, 23 of whom had a pneumonectomy and 14, a lobectomy. FEV_1 after pneumonectomy was predicted as accurately from the perfusion scan (mean percent error = 11% ± 10%) as from the ventilation scan (mean percent error = 14% ± 11%). FEV_1 after lobectomy could be predicted with a mean percent error of less than 10%. Because of these findings, all patients requiring lung resection had their postoperative FEV_1 predicted from the perfusion scan. Patients with a calculated postoperative FEV_1 of less than 1.0 L were considered medically inoperable. There were three deaths, one of which was related to pulmonary insufficiency, among 45 patients who underwent pneumonectomy with a predicted postoperative FEV_1 of greater than 1.0 L. Twenty-two of these patients had a preoperative FEV_1 of less than 2.0 L and would have not been considered candidates for pneumonectomy if preoperative function of each lung had been assumed to be equal. There were no surgically related deaths or cases of postoperative respiratory insufficiency among these patients. Forty patients, including seven with a preoperative FEV_1 of less than 1.5 L, underwent lobectomy, with no deaths or cases of postoperative respiratory insufficiency. *(Wernly JA, DeMeester TR, Kirchner PT, Myerowitz PD, Oxford DE, Golomb HM: Clinical value of quantitative ventilation-perfusion lung scans in the surgical management of bronchogenic carcinoma. J Thorac Cardiovasc Surg 1980;80:535–43).*

A Guide for Authors

Manuscripts should be sent to:
Nicholas M. Greene, M.D.
Editor in Chief
Anesthesia and Analgesia
Yale University School of Medicine
333 Cedar Street
New Haven, Connecticut 06510

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Manuscripts are accepted for consideration with the understanding that the material they present, including tables, figures, and data therein, has not been previously published and is not presently under consideration for publication elsewhere. Authors will be asked to transfer copyright of articles accepted for publication to the International Anesthesia Research Society.

Types of materials. The Journal publishes original articles, clinical reports, review articles, and letters to the editor. Original articles describe in 3000 words or less clinical or laboratory investigations. Clinical reports describe in 1000 words or less either (a) new and instructive case reports, or (b) anesthetic techniques or equipment of demonstrable originality, usefulness, and safety. Review articles of 2500 to 4000 words collate, describe, and evaluate previously published material for the establishment of new concepts. Letters to the editor, less than 300 words in length, include brief constructive comments concerning previously published articles or brief notations of general interest. Preliminary or incomplete reports are not accepted, nor are manuscripts containing fragments of material better incorporated into a single paper.

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Illustrations and other materials taken from other sources must be properly credited and assurance provided that permission for reproduction has been obtained from the copyright owner and author.

Editing. All papers will be edited for clarity, style, factual accuracy, internal logic, and grammar. Papers extensively copy edited will be returned to the author(s) for retyping. Editing will include the addition, following the Abstract, of key words for indexing purposes.

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Manuscripts must be prepared and submitted in the manner described in "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" as described in Annals of Internal Medicine 1979; 90: 95–9, and Lancet 1979; 1: 428–30.

Type manuscripts on white bond paper, 20.3 by 26.7 cm or 21.6 by 27.9 cm (8 by 10½ in or 8½ by 11 in) or ISO A4 (212 by 297 mm) with margins of at least 2.5 cm (1 in). Use double spacing throughout, including title page, abstract, text, acknowledgments, references, tables, and legends for illustrations.

Begin each of the following sections on separate pages: title page, abstract and key words, text, acknowledgments, references, tables (each table, complete with title and footnotes, on a separate page), and legends. Number pages consecutively, beginning with the title page. Type the page number in the upper right-hand corner of each page.

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Include numbers of observations and the statistical significance of the findings when appropriate. Detailed statistical analyses, mathematical derivations, and the like may sometimes be suitably presented in the form of one or more appendixes.

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Discussion. Emphasize the new and important aspects of the study and *conclusions* that follow from them. Do not repeat in detail data given in the Results section. Include in the Discussion the implications of the findings and their limitations and relate the observations to other relevant studies. Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not completely supported by your data. Avoid claiming priority and alluding to work that has not been completed. State new hypotheses when warranted, but clearly label them as such. Recommendations, when appropriate, may be included.

References. (The following style will appear in the journal effective volume 60, January 1981.) Number references consecutively in the order in which they are first mentioned in the text. Identify references in text, tables, and legends by arabic numerals (in parentheses). References cited *only* in tables or in legends to figures should be numbered in accordance with a sequence established by the first identification in the text of the particular table or illustration.

Use the form of references adopted by the U.S. National Library of Medicine and used in *Index Medicus*. Use the style of the examples cited at the end of this section, which have been approved by the National Library of Medicine.

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References must be verified by the author(s) against the original documents.

Examples of correct forms:

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1. Standard Journal Article (List all authors when six or less; when seven or more, list only first three and add et al)

   Soter NA, Wasserman SI, Austen KF. Cold urticaria: release into the circulation of histamine and eosinophil chemotactic factor of anaphylaxis during cold challenge. N Engl J Med 1976;294:687–90.

2. Corporate Author

   The Committee on Enzymes of the Scandinavian Society for Clinical Chemistry and Clinical Physiology. Recommended method for the determination of gamma-glutamyltransferase in blood. Scand J Clin Lab Invest 1976;36:119–25.

   Anonymous. Epidemiology for primary health care. Int J Epidemiol 1976;5:224–5.

Books and Other Monographs

3. Personal Author(s)

   Osler AG. Complement: mechanisms and functions. Englewood Cliffs: Prentice-Hall, 1976.

4. Corporate Author

   American Medical Association Department of Drugs. AMA drug evaluations. 3rd ed. Littleton: Publishing Sciences Group, 1977.

5. Editor, Compiler, Chairman as Author

   Rhodes AJ, Van Rooyen CE, comps. Textbook of virology: for students and practitioners of medicine and the other health sciences. 5th ed. Baltimore: Williams & Wilkins, 1968.

6. Chapter in Book

   Weinstein L, Swartz MN. Pathogenic properties of invading microorganisms. In: Sodeman WA Jr, Sodeman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: WB Saunders, 1974:457–72.

7. Agency Publication

   National Center for Health Statistics. Acute conditions: incidence and associated disability, United States July 1968–June 1969. Rockville, Md.: National Center for Health Statistics, 1972. (Vital and health statistics. Series 10: Data from the National Health Survey, no. 69) (DHEW publication no. (HSM)72-1036).

Tables. Type each table on a separate sheet; remember to double space. Do not submit tables as photographs. Number tables consecutively and supply a brief title for each. Give each column a short or abbreviated heading. Place explanatory matter in footnotes, not in the heading. Explain in footnotes all nonstandard abbreviations that are used in each table. For footnotes, use the following symbols in this sequence: *, †, ‡, §, ‖, ¶, ≠, **, ††. . . . Identify statistical measures of variation such as SD and SEM.

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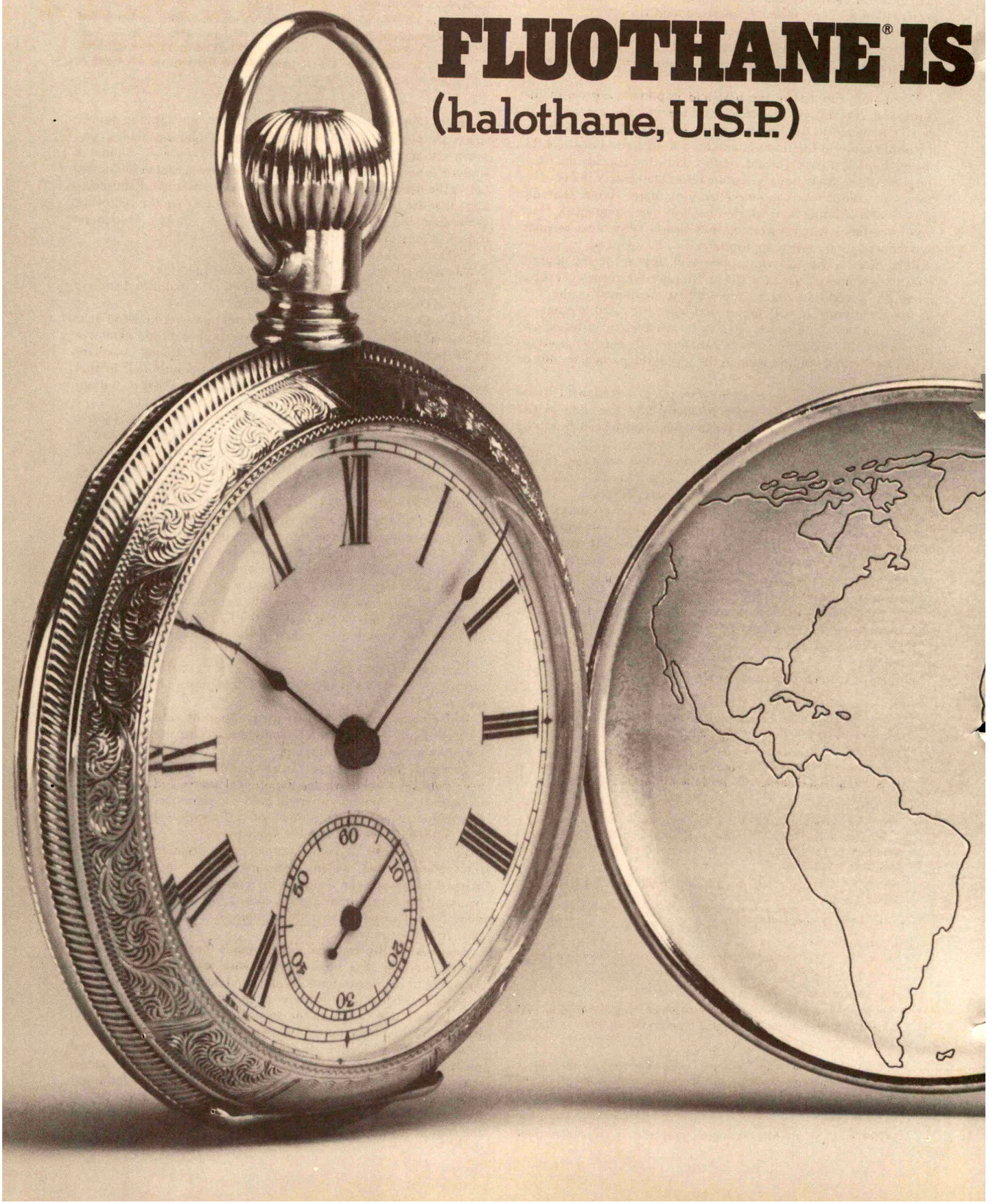
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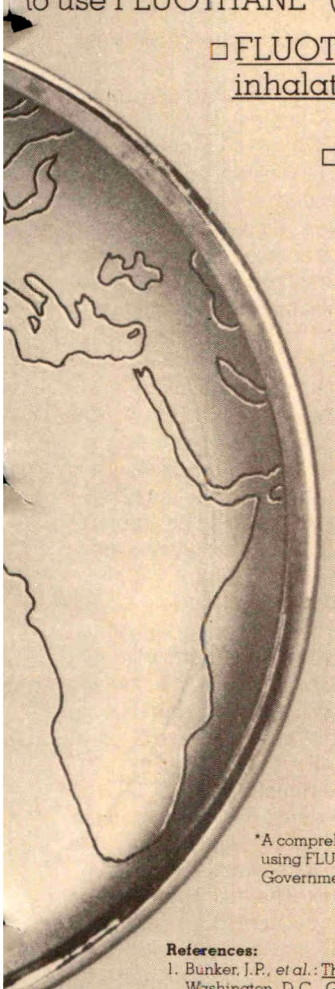
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*A comprehensive retrospective analysis covering 856,000 general anesthesias—nearly one-third using FLUOTHANE. Bunker, J.P., *et al.*: The National Halothane Study. Washington, D.C., Government Printing Office, 1969.

References:

1. Bunker, J.P., *et al.*: The National Halothane Study. Washington, D.C., Government Printing Office, 1969.
2. Brown, B.R., Sipes, I.G.: Biochem. Pharmacol. 26:2091-2094, 1977.
3. Steward, D.J.: Anesthesiology 43:268-276 (Aug.) 1975.
4. Proceedings, Virginia Society of Anesthesiologists, April 20-22, 1979, Richmond, VA.

See following page for Brief Summary.

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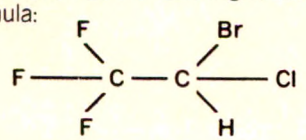
FLUOTHANE®
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(Complete text of package circular.)

Description. FLUOTHANE, brand of halothane, U.S.P., is an inhalation anesthetic. It is 2-bromo-2-chloro-1, 1, 1-trifluoroethane and has the following structural formula:



The specific gravity is 1.872-1.877 at 20° C, and the boiling point (range) is 49° C–51° C at 760 mm Hg. The vapor pressure is 243 mm Hg at 20° C. The blood/gas coefficient is 2.5 at 37° C, and the olive oil/water coefficient is 220 at 37° C. Vapor concentrations within anesthetic range are nonirritating and have a pleasant odor. FLUOTHANE is nonflammable, and its vapors mixed with oxygen in proportions from 0.5 to 50 per cent (v/v) are not explosive.

FLUOTHANE does not decompose in contact with warm soda lime. When moisture is present, the vapor attacks aluminum, brass, and lead, but not copper. Rubber, some plastics, and similar materials are soluble in FLUOTHANE; such materials will deteriorate rapidly in contact with FLUOTHANE vapor or liquid. Stability of FLUOTHANE is maintained by the addition of 0.01 per cent thymol (w/w), and storage is in amber colored bottles.

FLUOTHANE should not be kept indefinitely in vaporizer bottles not specifically designed for its use. Thymol does not volatilize along with FLUOTHANE, and therefore accumulates in the vaporizer, and may, in time, impart a yellow color to the remaining liquid or to wicks in vaporizers. The development of such discoloration may be used as an indicator that the vaporizer should be drained and cleaned, and the discolored FLUOTHANE (halothane, U.S.P.) discarded. Accumulation of thymol may be removed by washing with diethyl ether. After cleaning a wick or vaporizer, make certain all the diethyl ether has been removed before reusing the equipment to avoid introducing ether into the system.

Actions. FLUOTHANE is an inhalation anesthetic. Induction and recovery are rapid and depth of anesthesia can be rapidly altered. FLUOTHANE progressively depresses respiration. There may be tachypnea with reduced tidal volume and alveolar ventilation. FLUOTHANE is not an irritant to the respiratory tract, and no increase in salivary or bronchial secretions ordinarily occurs. Pharyngeal and laryngeal reflexes are rapidly obtunded. It causes bronchodilation. Hypoxia, acidosis, or apnea may develop during deep anesthesia.

FLUOTHANE reduces the blood pressure, and frequently decreases the pulse rate. The greater the concentration of the drug, the more evident these changes become. Atropine may reverse the bradycardia. FLUOTHANE does not cause the release of catecholamines from adrenergic stores. FLUOTHANE also causes dilation of the vessels of the skin and skeletal muscles.

Cardiac arrhythmias may occur during FLUOTHANE anesthesia. These include nodal rhythm, AV dissociation, ventricular extrasystoles and asystole. FLUOTHANE sensitizes the myocardial conduction system to the action of epinephrine and norepinephrine, and the combination may cause serious cardiac arrhythmias. FLUOTHANE increases cerebral spinal fluid pressure. FLUOTHANE produces moderate muscular relaxation. Muscle relaxants are used as adjuncts in order to maintain lighter levels of anesthesia. FLUOTHANE augments the action of nondepolarizing relaxants and ganglionic blocking agents. FLUOTHANE is a potent uterine relaxant.

Indications. FLUOTHANE (halothane, U.S.P.) is indicated for the induction and maintenance of general anesthesia.

Contraindications. FLUOTHANE is not recommended for obstetrical anesthesia except when uterine relaxation is required.

Warnings. When previous exposure to FLUOTHANE was followed by unexplained jaundice, consideration should be given to the use of other agents.

FLUOTHANE should be used in vaporizers that permit a reasonable approximation of output, and preferably of the calibrated type. The vaporizer should be placed out of circuit in closed circuit rebreathing systems; otherwise overdosage is difficult to avoid. The patient should be closely observed for signs of overdosage, *i.e.*, depression of blood pressure, pulse rate, and ventilation, particularly during assisted or controlled ventilation.

Usage in Pregnancy. Safe use of FLUOTHANE has not been established with respect to possible adverse effects upon fetal development. Therefore, FLUOTHANE should not be used in women where pregnancy is possible and particularly during early pregnancy, unless, in the judgment of the physician, the potential benefits outweigh the unknown hazards to the fetus.

Precautions. The uterine relaxation obtained with FLUOTHANE, unless carefully controlled, may fail to respond to ergot derivatives and oxytocic posterior pituitary extract.

FLUOTHANE increases cerebrospinal fluid pressure. Therefore, in patients with markedly raised intracranial pressure, if FLUOTHANE is indicated, administration should be preceded by measures ordinarily used to reduce cerebrospinal fluid pressure. Ventilation should be carefully assessed, and it may be necessary to assist or control ventilation to insure adequate oxygenation and carbon dioxide removal.

Epinephrine or norepinephrine should be employed cautiously, if at all, during FLUOTHANE (halothane, U.S.P.) anesthesia since their simultaneous use may induce ventricular tachycardia or fibrillation.

Nondepolarizing relaxants and ganglionic blocking agents should be administered cautiously, since their actions are augmented by FLUOTHANE.

Adverse Reactions. The following adverse reactions have been reported: mild, moderate and severe hepatic dysfunction (including hepatic necrosis), cardiac arrest, hypotension, respiratory arrest, cardiac arrhythmias, hyperpyrexia, shivering, nausea, and emesis.

Dosage and Administration. FLUOTHANE may be administered by the nonrebreathing technic, partial rebreathing, or closed technic. The induction dose varies from patient to patient. The maintenance dose varies from 0.5 per cent to 1.5 per cent.

FLUOTHANE may be administered with either oxygen or a mixture of oxygen and nitrous oxide.

How Supplied. No. 3125—Unit packages of 125 ml and 250 ml of halothane, U.S.P. stabilized with 0.01% thymol (w/w).

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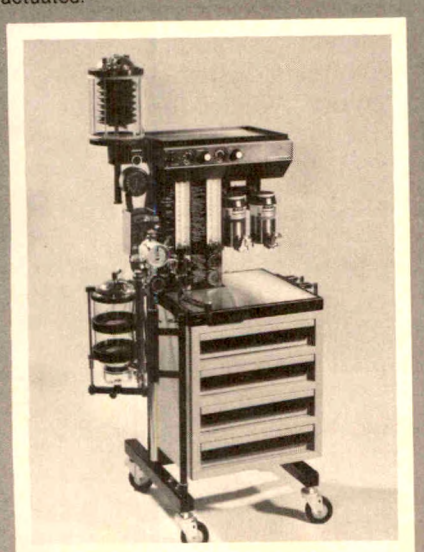
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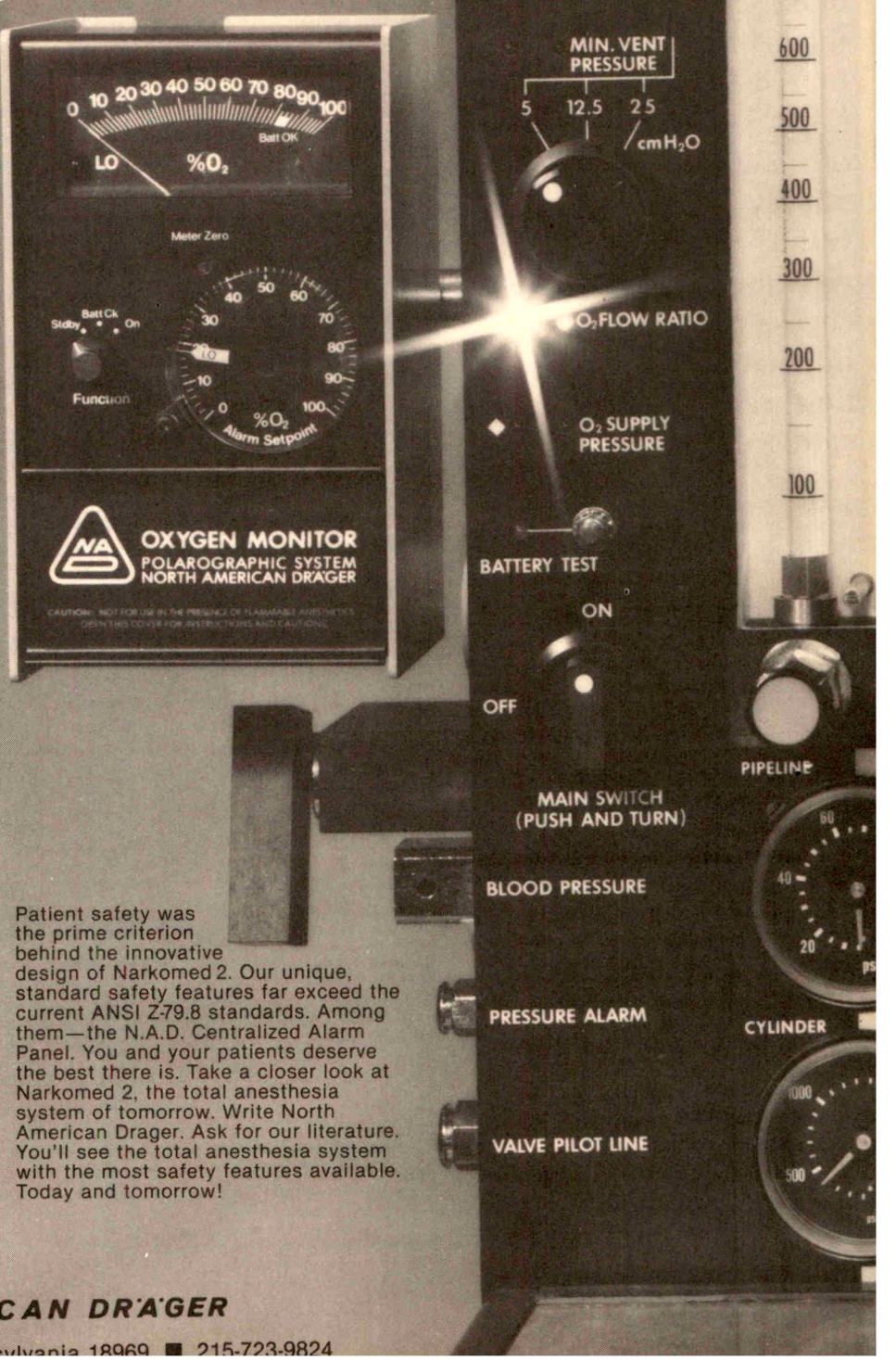
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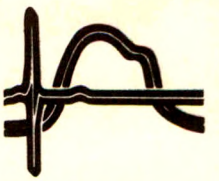
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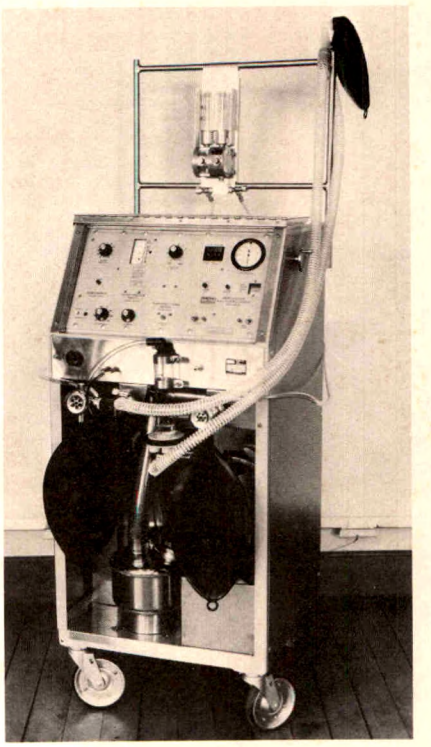
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EMERSON IMV Ventilator

A MAJOR ADVANTAGE

of Emerson ventilators is the sine-wave pressure curve produced by the Emerson piston.



Inspiratory flow starts slowly, increases to maximum at mid-breath, and slows down again to a kind of plateau at the end.

This flow pattern closely copies normal breathing, and (compared with a square wave) tends to distribute gas better in the lungs.* It probably accounts for the frequently-observed ability of Emersons to ventilate difficult patients at lower pressure levels.

Exhalation is exceptionally free. Thus, the positive phase is not prolonged needlessly, and impact on the cardiovascular system is minimized.

The lower mean intrathoracic pressure, that results from this sine-wave pattern and easy exhalation, is a circulatory benefit of outstanding clinical importance.

The simple, direct construction results in unique reliability. Emersons are known to operate for long periods without down-time or costly overhauls, a matter of significance for cost-effectiveness as well as for patient safety.

With characteristics that ensure ventilatory capacity and a minimum of circulatory interference, your Emerson can be called on to treat severely difficult cases. It can provide important benefits in routine cases as well.

*Sullivan, Saklad and Demers: "Ventilator Waveform and Gas Distribution" RESPIRATORY CARE 22:4:393.

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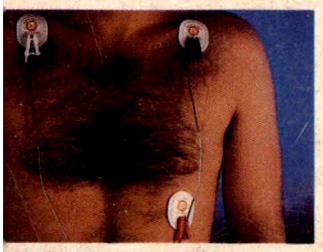
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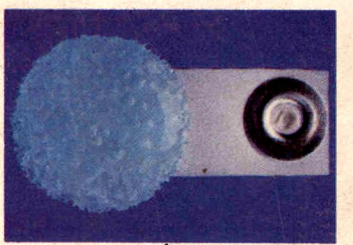
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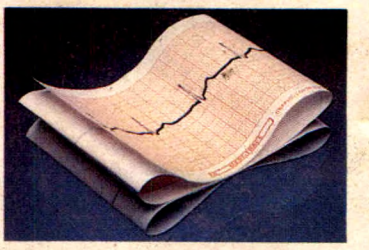
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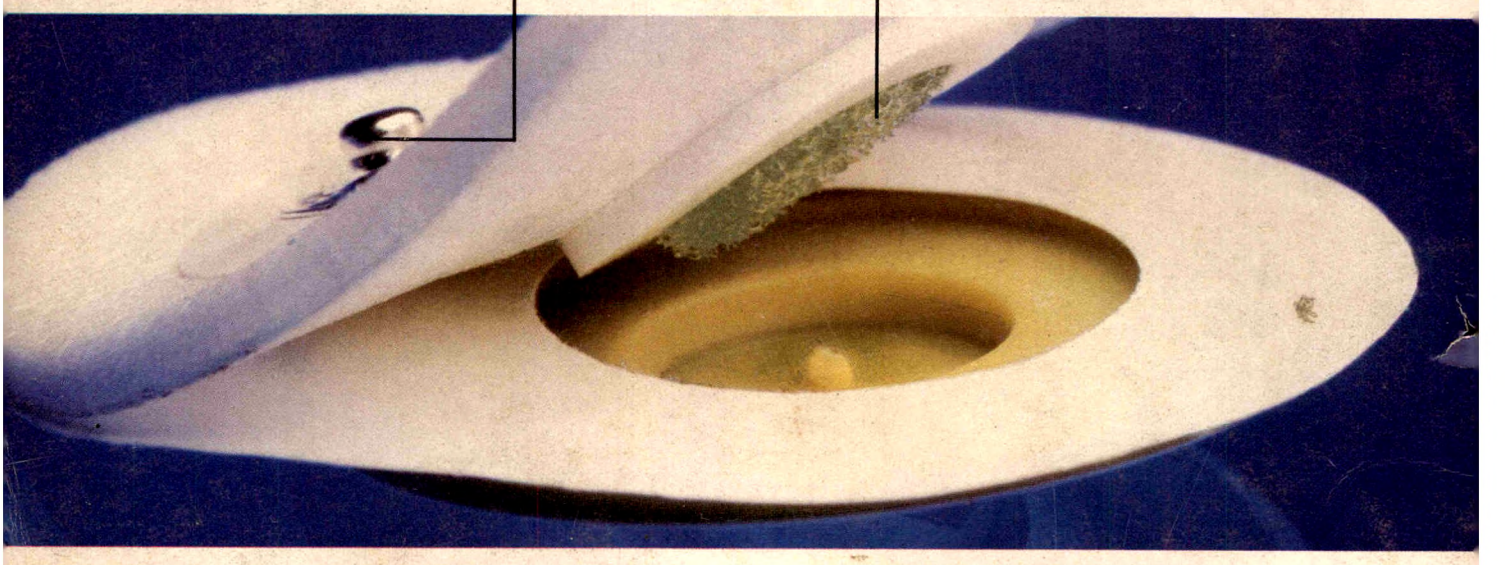
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ISSN 0003-2999
vol. 61, no. 1 January 1982

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Anesthesia and Analgesia

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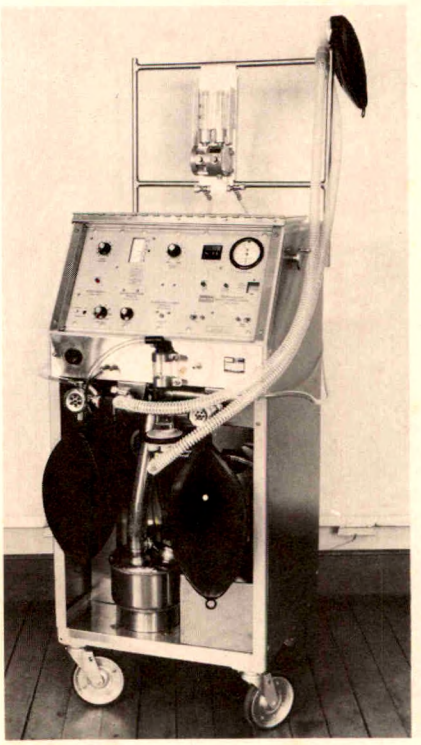
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Anesthesia and Analgesia

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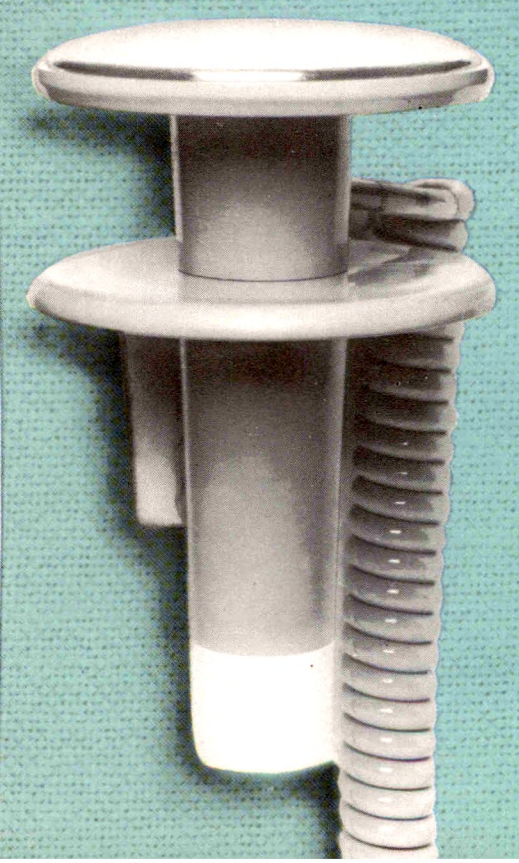
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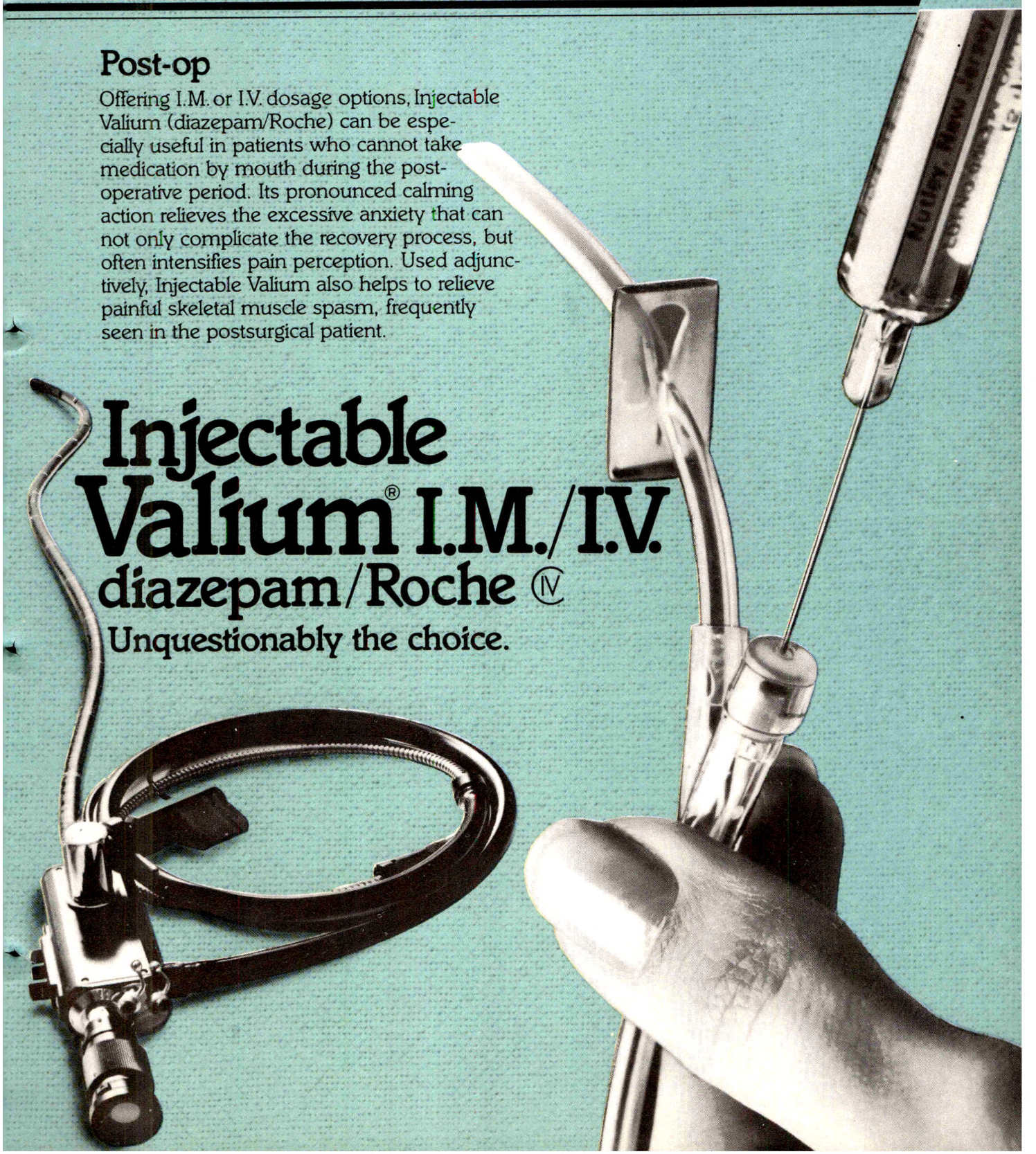
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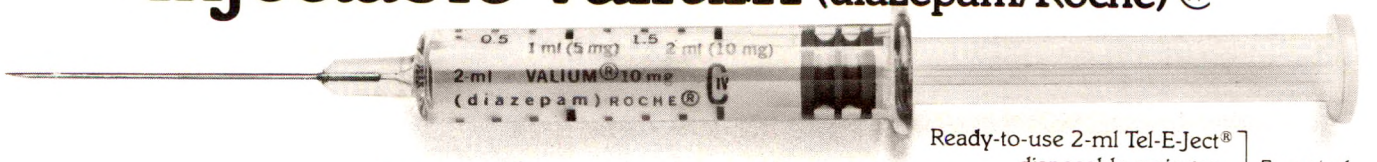
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Indications: Management of anxiety disorders, or short-term relief of symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic. Symptomatic relief of acute agitation, tremor, impending or acute delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in: relief of skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; tetanus; status epilepticus, severe recurrent seizures; adjunctively in anxiety, tension or acute stress reactions prior to endoscopic/surgical procedures; cardioversion.

Contraindications: Hypersensitivity; acute narrow angle glaucoma; may be used in paitents with open angle glaucoma receiving appropriate therapy.

Warnings: *To reduce the possibility of venous thrombosis, phlebitis, local irritation, swelling, and, rarely, vascular impairment when used I.V.: inject slowly, taking at least one minute for each 5 mg (1 ml) given; do not use small veins, i.e., dorsum of hand or wrist; use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute Valium (diazepam/Roche) with other solutions or drugs in syringe or infusion flask. If it is not feasible to administer Valium directly I.V., it may be injected slowly through the infusion tubing as close as possible to the vein insertion.*

Administer with extreme care to elderly, very ill, those with limited pulmonary reserve because of possibility of apnea and/or cardiac arrest; concomitant use of barbiturates, alcohol or other CNS depressants increases depression with increased risk of apnea; have resuscitative facilities available. When used with narcotic analgesic, eliminate or reduce narcotic dosage at least ⅓, administer in small increments. Should not be administered to patients in shock, coma, acute alcoholic intoxication with depression of vital signs. As with most CNS-acting drugs, caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).

Has precipitated tonic status epilepticus in patients treated for petit mal status or petit mal variant status.

Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation after long use of excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after long, continuous use at high therapeutic levels. After extended therapy, gradually taper dosage.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations, as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Not recommended for OB use.

Efficacy/safety not established in neonates (age 30 days or less); prolonged CNS depression observed. In children, give slowly (up to 0.25 mg/kg over 3 minutes) to avoid apnea or prolonged somnolence; can be repeated after 15 to 30 minutes. If no relief after third administration, appropriate adjunctive therapy is recommended.

Precautions: Although promptly controlled, seizures may return; readminister if necessary; not recommended for long-term maintenance therapy.

If combined with other psychotropics or anticonvulsants, carefully consider individual pharmacologic effects—particularly with known compounds which may potentiate action of Valium (diazepam/Roche), *i.e.*, phenothiazines, narcotics, barbiturates, MAO inhibitors, antidepressants. Protective measures indicated in highly anxious patients with accompanying depression who may have suicidal tendencies. Observe usual precautions in impaired hepatic function; avoid accumulation in patients with compromised kidney function. Laryngospasm/increased cough reflex are possible during peroral endoscopic procedures; use topical anesthetic, have necessary countermeasures available. Hypotension or muscular weakness possible, particularly when used with narcotics, barbiturates or alcohol. Use lower doses (2 to 5 mg) for elderly/debilitated.

The clearance of Valium and certain other benzodiazepines can be delayed in association with Tagamet (cimetidine) administration. The clinical significance of this is unclear.

Adverse Reactions: Drowsiness, fatigue, ataxia, venous thrombosis/phlebitis at injection site, confusion, depression, dysarthria, headache, hypoactivity, slurred speech, syncope, tremor, vertigo, constipation, nausea, incontinence, changes in libido, urinary retention, bradycardia, cardiovascular collapse, hypotension, blurred vision, diplopia, nystagmus, urticaria, skin rash, hiccups, changes in salivation, neutropenia, jaundice. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Cough, depressed respiration, dyspnea, hyperventilation, laryngospasm/pain in throat and chest have been reported in peroral endoscopic procedures. Isolated reports of neutropenia, jaundice; periodic blood counts, liver function tests advisable during long-term therapy. Minor EEG changes, usually low-voltage fast activity, of no known significance.

Dosage: Usual initial dose in older children and adults is 2 to 20 mg I.M. or I.V., depending on indication and severity. Larger doses may be required in some conditions (tetanus). In acute conditions injection may be repeated within 1 hour, although interval of 3 to 4 hours is usually satisfactory. Lower doses (usually 2 to 5 mg) with slow dosage increase for elderly or debilitated patients and when sedative drugs are added. (See Warnings and Adverse Reactions.)

For dosages in infants and children see below; have resuscitative facilities available.

I.M. use: by deep injection into the muscle.

I.V. use: inject slowly, take at least one minute for each 5 mg (1 ml) given. Do not use small veins, i.e., dorsum of hand or wrist. Use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute Valium (diazepam/Roche) with other solutions or drugs in syringe or infusion flask. If it is not feasible to administer Valium directly I.V., it may be injected slowly through the infusion tubing as close as possible to the vein insertion.

Moderate anxiety disorders and symptoms of anxiety, 2 to 5 mg I.M. or I.V. and severe anxiety disorders and symptoms of anxiety, 5 to 10 mg I.M. or I.V., repeat in 3 to 4 hours if necessary; acute alcoholic withdrawal, 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary. Muscle spasm, in adults, 5 to 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary (tetanus may require larger doses); in children, *administer I.V. slowly;* for tetanus in infants over 30 days of age, 1 to 2 mg I.M. or I.V., repeat every 3 to 4 hours if necessary; in children 5 years or older, 5 to 10 mg repeated every 3 to 4 hours as needed. Respiratory assistance should be available.

Status epilepticus, severe recurrent convulsive seizures (I.V. route preferred), 5 to 10 mg adult dose administered slowly, repeat at 10- to 15-minute intervals up to 30 mg maximum. Repeat in 2 to 4 hours if necessary keeping in mind possibility of residual active metabolites. Use caution in presence of chronic lung disease or unstable cardiovascular status. Infants (over 30 days) and children (under 5 years), 0.2 to 0.5 mg slowly every 2 to 5 min., up to 5 mg (I.V. preferred). Children 5 years plus, 1 mg every 2 to 5 min., up to 10 mg (slow I.V. preferred); repeat in 2 to 4 hours if needed. EEG monitoring may be helpful.

In endoscopic procedures, titrate I.V. dosage to desired sedative response, generally 10 mg or less but up to 20 mg (if narcotics are omitted) immediately prior to procedure; if I.V. cannot be used, 5 to 10 mg I.M. approximately 30 minutes prior to procedure. As preoperative medication, 10 mg I.M.; in cardioversion, 5 to 15 mg I.V. within 5 to 10 minutes prior to procedure. Once acute symptomatology has been properly controlled with injectable form, patient may be placed on oral form if further treatment is required.

Management of Overdosage: Manifestations include somnolence, confusion, coma, diminished reflexes. Monitor respiration, pulse, blood pressure; employ general supportive measures, I.V. fluids, adequate airway. Hypotension may be combated by the use of levarterenol or metaraminol. Dialysis is of limited value.

Supplied: Ampuls, 2 ml, boxes of 10; Vials, 10 ml, boxes of 1; Tel-E-Ject® (disposable syringes), 2 ml, boxes of 10. Each ml contains 5 mg diazepam compounded with 40% propylene glycol, 10% ethyl alcohol, 5% sodium benzoate and benzoic acid as buffers, and 1.5% benzyl alcohol as preservative.

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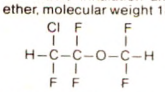
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$T=°C+273.16$ (Kelvin)

The specific gravity (25°/25°C) is 1.517. The refractive index at 20° is 1.3026-1.3030. The blood/gas coefficient is 1.91 at 37°C and the oil/gas coefficient is 98.5 at 37°C. The M.A.C. (minimum alveolar concentration) in man is 1.68 percent in pure oxygen, 0.57 in 70% nitrous oxide and oxygen, and 1.17 in 30% nitrous oxide and oxygen.

ETHRANE is a clear, colorless, stable liquid whose purity exceeds 99.9 percent (area % by gas chromatography). No chemical stabilizers are added as these have been found, through controlled laboratory tests, to be unnecessary to maintain stability even in the presence of ultraviolet light. ETHRANE is stable to strong base and does not decompose in contact with soda lime and does not attack aluminum, tin, brass, iron or copper. The partition coefficients of ETHRANE at 25°C are 74 in conductive rubber and 120 in polyvinyl chloride.

CLINICAL PHARMACOLOGY

ETHRANE (enflurane) is an inhalation anesthetic. Induction and recovery from anesthesia with ETHRANE are rapid. ETHRANE has a mild, sweet odor. There is mild stimulus to salivation or tracheobronchial secretions when ETHRANE is used alone. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia changes rapidly with ETHRANE. ETHRANE reduces ventilation as depth of anesthesia increases. High pCO_2 levels can be obtained at deeper levels of anesthesia if ventilation is not supported. ETHRANE provokes a sigh response reminiscent of that seen with diethyl ether.

There is a decrease in blood pressure with induction of anesthesia, followed by a return to near normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding increases in hypotension. Heart rate remains relatively constant without significant bradycardia. Electrocardiographic monitoring or recordings indicate that cardiac rhythm remains stable. Elevation of the carbon dioxide level in arterial blood does not alter cardiac rhythm.

Studies in man indicate a considerable margin of safety in the administration of epinephrine containing solutions during ETHRANE anesthesia. ETHRANE anesthesia has been used in excision of pheochromocytoma in man without ventricular arrhythmias. On the basis of studies in patients anesthetized with ETHRANE and injected with epinephrine containing solutions to achieve hemostasis in a highly vascular area (transphenoidal surgery), it is recommended that 2 micrograms per kilogram (2μg/kg) of epinephrine may be injected subcutaneously over a 10 minute period. This may be repeated up to 3 times per hour.

Example: Up to 10 ml of 1:100,000 epinephrine containing solution (10μg/ml) may be injected subcutaneously over a 10 minute period in a 50 kilogram patient judged to have ordinary tolerance to epinephrine administration. No more than 30 ml of 1:100,000 epinephrine containing solution (10μg/ml) should be administered to such a patient per hour. The concomitant administration of lidocaine enhances the safety of the use of epinephrine during ETHRANE anesthesia. This effect of lidocaine is dose related. All customary precautions in the use of vasoconstrictor substances should be observed.

Example Two: Alternatively, up to 20 ml of 1:200,000 epinephrine containing solution (5 μg/ml) may be substituted for 10 ml of 1:100,000 solution in the above example.

Muscle relaxation may be adequate for intra-abdominal operation at normal levels of anesthesia. Muscle relaxants may be used to achieve greater relaxation and all commonly used muscle relaxants are compatible with ETHRANE. The NONDEPOLARIZING MUSCLE RELAXANTS ARE POTENTIATED. In the normal 70 kg adult, 6 to 9 mg of d-tubocurarine or 1 to 1.5 mg of pancuronium will produce a 90 percent or greater depression of twitch height. Neostigmine does not reverse the direct effect of ETHRANE.

Biotransformation of ETHRANE in man results in low levels of serum fluoride ions averaging 15 μM/L. These levels are well below the 50 μM/L threshold level which can produce minimal renal damage in normal subjects; however, it is possible that these levels could result in damage in patients with severely impaired renal function or those undergoing renal transplantation. Depression of lymphocyte transformation does not follow prolonged ETHRANE anesthesia in man in the absence of surgery. Thus ETHRANE does not depress this aspect of the immune response.

INDICATIONS

ETHRANE (enflurane) may be used for induction and maintenance of general anesthesia. Adequate data have not been developed to establish its application in obstetrical anesthesia.

CONTRAINDICATIONS

Seizure disorders (see WARNINGS).

Known sensitivity to ETHRANE (enflurane) or other halogenated anesthetics.

WARNINGS

Increasing depth of anesthesia with ETHRANE (enflurane) may produce a change in the electroencephalogram characterized by high voltage, fast frequency, progressing through spike-dome complexes alternating with periods of electrical silence to frank seizure activity. The latter may or may not be associated with motor movement. Motor activity, when encountered, generally consists of twitching or "jerks" of various muscle groups; it is self-limiting and can be terminated by lowering the anesthetic concentration. This electroencephalographic pattern associated with deep anesthesia is exacerbated by low arterial carbon dioxide tension. A reduction in ventilation and anesthetic concentration usually suffices to eliminate seizure activity. Cerebral blood flow and metabolism studies in normal volunteers immediately following seizure activity show no evidence of cerebral hypoxia. Mental function testing does not reveal any impairment of performance following prolonged ETHRANE anesthesia associated with or not associated with seizure activity.

Since levels of anesthesia may be altered easily and rapidly, only calibrated vaporizers which measure output with reasonable accuracy should be used. Hypotension and respiratory exchange can serve as a guide to anesthesia depth. Deep levels of anesthesia may produce marked hypotension and respiratory depression.

The action of nondepolarizing relaxants is augmented by ETHRANE. Less than the usual amounts of these drugs should be used. If the usual amounts of nondepolarizing relaxants are given, the time for recovery from myoneural blockade will be longer in the presence of ETHRANE than for other commonly used anesthetics.

Usage in Pregnancy: Safety in pregnancy has not been established. Reproduction studies have been performed in rats and rabbits, and there is no evidence of harm to the animal fetus. The relevance of these studies to the human is not known. Since there is no adequate experience in pregnant women who have received the drug, safety in pregnancy has not been established.

PRECAUTIONS

Bromsulfalein (BSP) retention is mildly elevated postoperatively in some cases. This may relate to the effect of surgery since prolonged anesthesia (5 to 7 hours) in human volunteers does not result in BSP elevation. There is some elevation of glucose and white blood count intraoperatively. Glucose elevation should be considered in diabetic patients. ETHRANE (enflurane) should be used with caution in patients who by virtue of medical or drug history could be considered more susceptible to cortical stimulation produced by this drug. As with other general anesthetics and some muscle relaxants, hyperpyrexia has been observed with the use of ETHRANE.

ADVERSE REACTIONS

1. Motor activity examplified by movements of various muscle groups and/or seizures may be encountered with deep levels of ETHRANE (enflurane) anesthesia, or light levels with hypocapnia.
2. Hypotension and respiratory depression have been reported.
3. Arrhythmias, shivering, nausea, and vomiting have been reported.
4. Elevation of the white blood count has been observed.

DOSAGE AND ADMINISTRATION

The concentration of ETHRANE (enflurane) being delivered during anesthesia from a vaporizer should be known. This may be accomplished by using:

a) vaporizers calibrated specifically for ETHRANE.

b) vaporizers from which delivered flows can easily and readily be calculated.

Nothing is present in the agent to alter calibration or affect the operation characteristics of the vaporizer.

Preanesthetic Medication: Preanesthetic medication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by ETHRANE and the heart rate remains constant. the use of anticholinergic drugs is a matter of choice.

Induction: Induction may be achieved using ETHRANE alone with oxygen or in combination with oxygen-nitrous oxide mixtures. Under these conditions some excitement may be encountered. If excitement is to be avoided, a hypnotic dose of a short-acting barbiturate should be used to induce unconsciousness, followed by the ETHRANE mixture. In general, inspired concentrations of 2.0-4.5% ETHRANE produce surgical anesthesia in 7-10 minutes.

Maintenance: Surgical levels of anesthesia may be maintained with 0.5-3% ETHRANE. Maintenance concentrations should not exceed 3%. If added relaxation is required, supplemental doses of muscle relaxants may be used. Ventilation to maintain the tension of carbon dioxide in arterial blood in the 35-45 mm Hg range is preferred. Hyperventilation should be avoided in order to minimize possible CNS excitation.

The level of blood pressure during maintenance is an inverse function of ETHRANE concentration in the absence of other complication problems. Excessive decreases (unless related to hypovolemia) may be due to depth of anesthesia and in such instances should be corrected by lightening the level of anesthesia.

Overdosage: In the event of overdosage, or what may appear to be overdosage, the following action should be taken.

Stop drug administration; establish a clear airway and initiate assisted or controlled ventilation with pure oxygen.

PACKAGING

ETHRANE (enflurane) is packaged in 125 and 250 ml amber colored bottles.

Ohio Medical Anesthetics

A Division of Airco, Inc.
3030 Airco Drive, P.O. Box 7550, Madison, Wisconsin 53707
Cable Address: OHIOMED • International Telex: 910-286-2712



The Vitatek 511™ Monitor

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Innovation. You can see it throughout the Vitatek 511. In the unique features, like BRITELINE™, the new enhanced non-fade display mode. In the expanded capabilities, like trending, on CRT and optional recorder.

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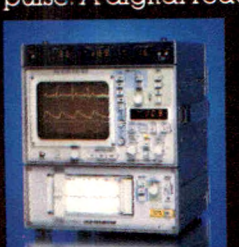
The Vitatek 408 Adult Monitor

An economical, single-trace instrument designed for ECG measurement. The Vitatek 408 provides heart-rate reading (triggered sweep), with high and low heart-rate alarms. There is three-lead selection and full lead is optional. It's compact, lightweight, battery and line (AC) operable — extremely portable. An optional recorder is available.



The Vitatek 414 Adult Monitor

A dual or three-trace monitor with simultaneous display of ECG and blood pressure or peripheral pulse. A digital readout shows heart rate, systolic/diastolic blood pressures, mean blood pressure or temperature. Options are available for pressure gauge factor, ECG full-lead select, electrosurgical suppression, recorder and digital readout module.



The Vitatek 413A Neonatal Monitor

A three-trace instrument designed especially for neonatal monitoring. It simultaneously displays ECG, blood pressure or peripheral pulse, and respiration waveforms. A selectable digital readout shows heart rate, respiration rate, systolic/diastolic or mean blood pressure, two temperatures or temperature difference. An optional recorder is available in addition to a digital readout module.



Now from Vitatek ... Everything you've come to expect from Tektronix ... plus

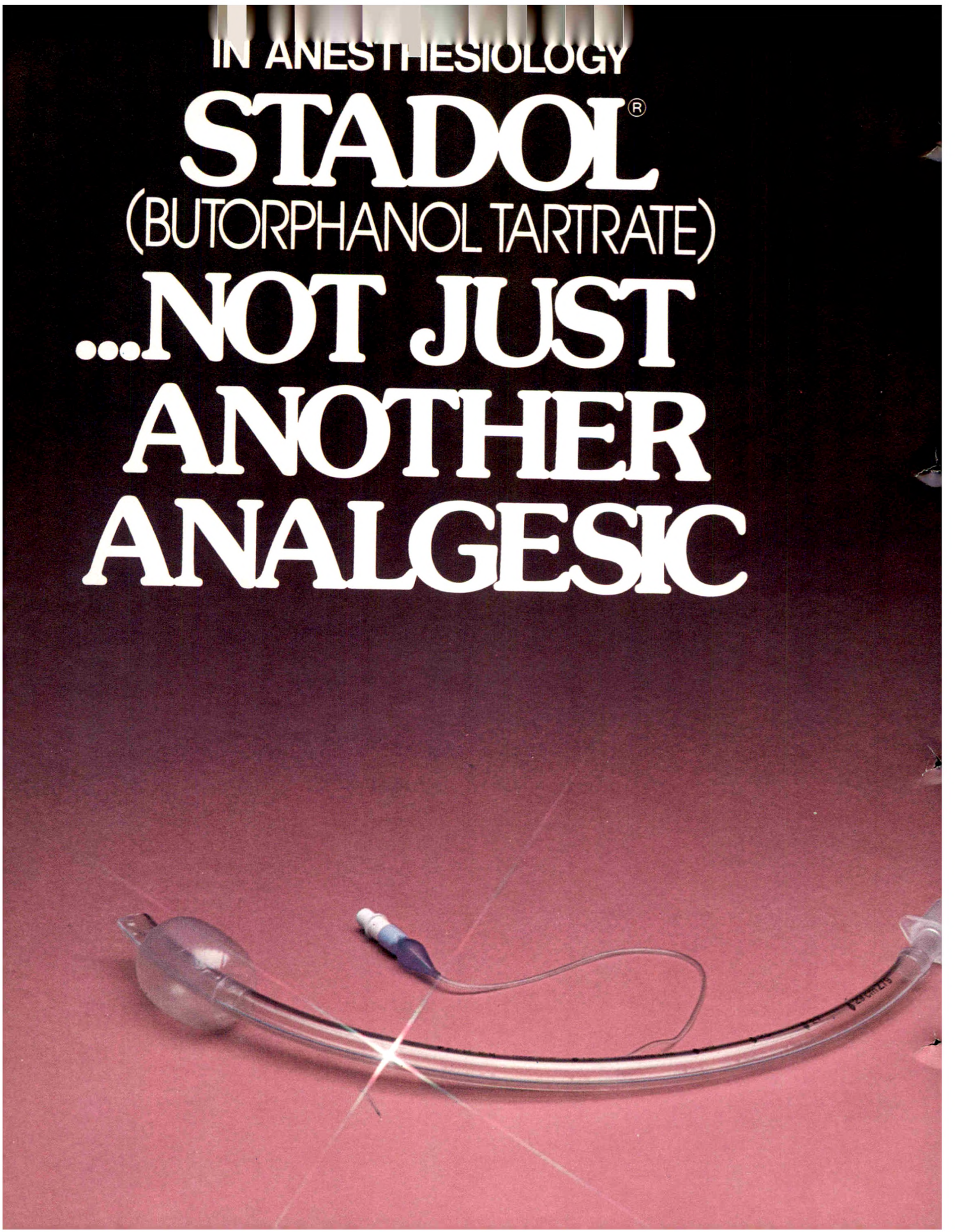
Vitatek is the new name for what was formerly the portable patient monitoring division of Tektronix. But the only thing that's changed is our name. The people, the skills, the experience, the quality standards, the commitment to excellence — these haven't changed. As a member company of the Squibb Medical Systems Group, we have only added valuable new dimensions to our capabilities and resources.

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In anesthesiology, you need more than just an effective analgesic. You need an analgesic with a proven safety margin. Stadol offers unexcelled efficacy...potency equivalent to morphine and meperidine...and a rapid onset of action. But, the main reason anesthesiologists like yourself are turning to Stadol is the safety difference it provides:

PREOPERATIVELY

- good sedative effect
- reduces apprehension
- compatible with many premedicants such as atropine, hydroxyzine, promethazine, glycopyrrolate

INTRAOPERATIVELY

- adaptable to a wide range of surgical procedures
- provides smooth induction and emergence from anesthesia
- rapid return to spontaneous respiration
- rarely requires reversal by naloxone

POSTOPERATIVELY

- limited respiratory depression potential*
- minimal hypotensive effect
- little nausea or vomiting

Note: Stadol should not be administered to patients who have significant recent narcotic experience; its narcotic antagonist properties may induce withdrawal reactions unless detoxification is accomplished prior to use.



*2 mg Stadol produces a degree of respiratory depression similar to that of 10 mg morphine or 70 mg meperidine. Unlike these other agents, doubling the Stadol dose to 4 mg does not appreciably increase the magnitude of respiratory depression.

Please see brief summary of prescribing information on the following page.

BRISTOL™

Bristol Laboratories
Division of Bristol-Myers Company
Syracuse, New York 13201

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Stadol® IM IV
(butorphanol tartrate)

for moderate to severe pain...
the effective analgesic with
the safety difference

Stadol® IM IV
(butorphanol tartrate)

the effective analgesic with the safety difference

Brief Summary of Prescribing Information
STADOL® (butorphanol tartrate)
For complete information, consult Official Package Circular.

(2) 12/10/79

INDICATIONS AND USAGE—Stadol is recommended for the relief of moderate to severe pain. Stadol can also be used for preoperative or preanesthetic medication, as a supplement to balanced anesthesia, and for the relief of prepartum pain.

CONTRAINDICATIONS—Stadol should not be administered to patients who have been shown to be hypersensitive to it.

WARNINGS—Patients Physically Dependent on Narcotics: Because of its antagonist properties, Stadol is not recommended for patients physically dependent on narcotics. Detoxification in such patients is required prior to use.
Due to the difficulty in assessing addiction in patients who have recently received substantial amounts of narcotic medication, caution should be used in the administration of Stadol. Detoxification of such patients prior to usage should be carefully considered.

Drug Dependence: Special care should be exercised in administering Stadol to emotionally unstable patients and to those with a history of drug misuse. When long-term therapy is contemplated, such patients should be closely supervised. Even though Stadol has a low physical dependence liability, care should be taken that individuals who may be prone to drug abuse are closely supervised. It is important to avoid increases in dose and frequency of injections by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

Head Injury and Increased Intracranial Pressure: Although there is no clinical experience in patients with head injury, it can be assumed that Stadol, like other potent analgesics, elevates cerebrospinal fluid pressure. Therefore the use of Stadol in cases of head injury can produce effects (e.g., miosis) which may obscure the clinical course of patients with head injuries. In such patients Stadol must be used with extreme caution and only if its use is deemed essential.

Cardiovascular Effects: Because Stadol increases the work of the heart, especially the pulmonary circuit, the use of this drug in acute myocardial infarction or in cardiac patients with ventricular dysfunction or coronary insufficiency should be limited to those who are hypersensitive to morphine sulfate or meperidine.

PRECAUTIONS—Certain Respiratory Conditions: Because Stadol causes some respiratory depression, it should be administered only with caution and low dosage to patients with respiratory depression (e.g., from other medication, uremia, or severe infection), severely limited respiratory reserve, bronchial asthma, obstructive respiratory conditions, or cyanosis.

Impaired Renal or Hepatic Function: Although laboratory tests have not indicated that Stadol causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Extensive liver disease may predispose to greater side effects and greater activity from the usual clinical dose, possibly the result of decreased metabolism of the drug by the liver.

Biliary Surgery: Clinical studies have not been done to establish the safety of Stadol administration to patients about to undergo surgery of the biliary tract.

Usage as a Preoperative or Preanesthetic Medication: Slight increases in systolic blood pressure may occur, therefore caution should be employed when Stadol is used in the hypertensive patient.

Usage in Baianced Anesthesia: The use of pancuronium in combination with Stadol may cause an increase in conjunctival changes.

Usage in Pregnancy: The safety of Stadol for use in pregnancy prior to the labor period has not been established; therefore, this drug should be used in pregnant patients only when in the judgment of the physician its use is deemed essential to the welfare of the patient.

Reproduction studies have been performed in rats, mice and rabbits and have revealed no evidence of impaired fertility or harm to the fetus due to Stadol at about 2.5 to 5 times the human dose.

Usage in Labor and Delivery: Safety to the mother and fetus following administration of Stadol during labor has been established. Patients receiving Stadol during labor have experienced no adverse effects other than those observed with commonly used analgesics. Stadol should be used with caution in women delivering premature infants.

Usage in Nursing Mothers: The use of Stadol in lactating mothers who are nursing their infants is not recommended since it is not known whether this drug is excreted in human milk. Stadol has been used safely for labor pain in mothers who subsequently nursed their infants.

Usage in Children: Safety and efficacy in children below age 18 years have not been established.

ADVERSE REACTIONS—The most frequent adverse reactions in 1250 patients treated with Stadol are: sedation (503, 40%), nausea (82, 6%), clammy/sweating (76, 6%).
Less frequent reactions are: headache (35, 3%), vertigo (33, 3%), floating feeling (33, 3%), dizziness (23, 2%), lethargy (19, 2%), confusion (15, 1%), lightheadedness (12, 1%).
Other adverse reactions which may occur (reported incidence of less than 1%) are:
CNS: nervousness, unusual dreams, agitation, euphoria, hallucinations
Autonomic: flushing and warmth, dry mouth, sensitivity to cold
Cardiovascular: palpitation, increase or decrease of blood pressure
Gastrointestinal: vomiting
Respiratory: slowing of respiration, shallow breathing
Dermatological: rash or hives
Eye: diplopia or blurred vision

OVERDOSAGE—Manifestations: Although there have been no experiences of overdosage with Stadol during clinical trials, this may occur due to accidental or intentional misuse as well as therapeutic use. Based on the pharmacology of Stadol, overdosage could produce some degree of respiratory depression and variable cardiovascular and central nervous system effects.

Treatment: The immediate treatment of suspected Stadol overdosage is intravenous naloxone. The respiratory and cardiac status of the patient should be evaluated constantly and appropriate supportive measures instituted, such as oxygen, intravenous fluids, vasopressors and assisted or controlled respiration.

HOW SUPPLIED—Stadol (butorphanol tartrate) Injection for I.M. or I.V. use, is available as follows:

NDC 0015-5644-20—2 mg per ml, 2-ml vial
NDC 0015-5645-20—1 mg per ml, 1-ml vial
NDC 0015-5646-20—2 mg per ml, 1-ml vial
NDC 0015-5646-23—2 mg per ml, 1-ml Disposable Syringe
NDC 0015-5648-20—2 mg per ml, 10-ml multi-dose vial

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Bristol Laboratories
Division of Bristol-Myers Company
Syracuse, New York 13201

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When it comes to infection control, this Ohio® mask has a clear advantage.



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The Ohio Disposable Mask is transparent. It maximizes visual access to your patient.

You instantly see expelled foreign matter in the mask. So you can take fast, corrective measures to prevent aspiration and assure airway patency.

By monitoring lip color and watching the formation of condensation on this transparent mask, you can get a better grasp of your patient's clinical status. You view clouding and clearing of the cone with each breath. And you study lip color to analyze both temperature and relative oxygen perfusion.

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The Ohio Disposable Mask is available in three sizes to fit a wide variety of facial features.

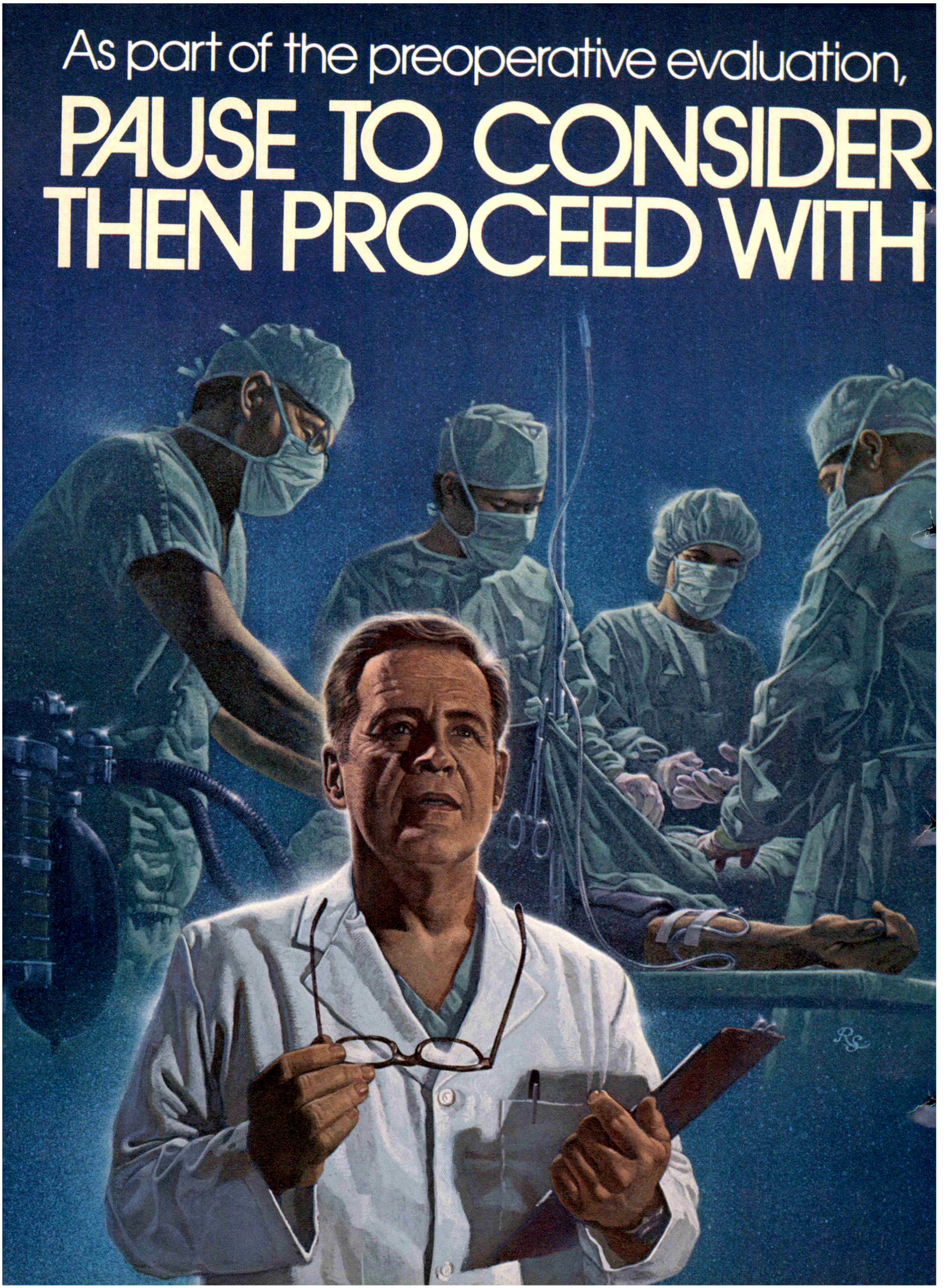
The soft, malleable cushion holds its shape to help provide a tight seal and minimize facial marking. And the shape of the cone makes holding the mask easier, less tiresome for you.

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THEN PROCEED WITH

THE RECORD, PAVULON® nondepolarizing muscle relaxant (pancuronium bromide injection)

Pavulon was introduced into the United States after four years of documented success in Europe.

Now, after more than a decade, the Pavulon record of superior performance, efficacy and safety continues.

Pavulon has been used successfully in a wide variety of surgical procedures involving all patient types—from the neonate to the elderly—from the poor risk patient to the good risk patient. In addition, Pavulon has proved a valuable adjunct in the management of mechanically ventilated patients in intensive care units.

A Record of Success
PAVULON®
(pancuronium bromide injection)

Please see next page for brief summary of prescribing information.

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Organon Pharmaceuticals
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West Orange, N.J. 07052

A Record of Success

PAVULON® nondepolarizing muscle relaxant (pancuronium bromide injection)

BRIEF SUMMARY
(Please consult package insert for full prescribing information.)

THIS DRUG SHOULD ONLY BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

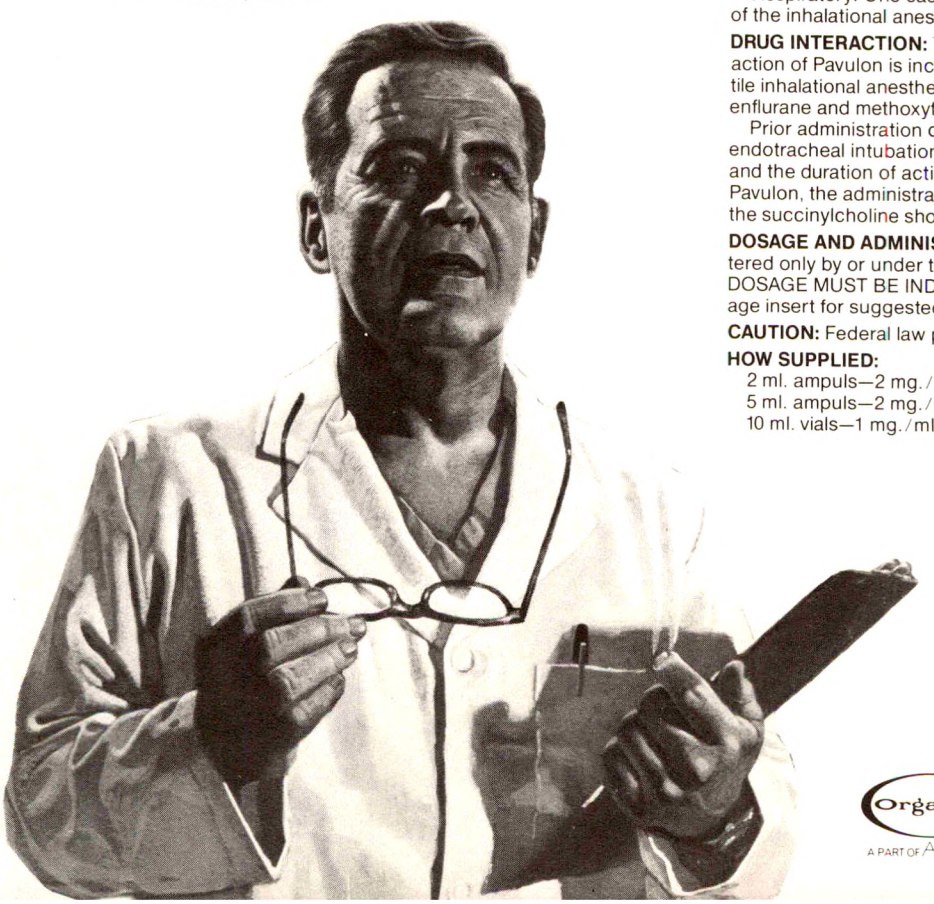
ACTIONS: Pavulon is a non-depolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform) on the myoneural junction.

Pavulon (pancuronium bromide) is antagonized by acetylcholine, anticholinesterases, and potassium ion. Its action is increased by inhalational anesthetics such as halothane, diethyl ether, enflurane and methoxyflurane, as well as quinine, magnesium salts, hypokalemia, some carcinomas, and certain antibiotics such as neomycin, streptomycin, clindamycin, kanamycin, gentamicin and bacitracin. The action of Pavulon may be altered by dehydration, electrolyte imbalance, acid-base imbalance, renal disease, and concomitant administration of other neuromuscular agents.

CONTRAINDICATIONS: Pavulon is contraindicated in patients known to be hypersensitive to the drug or to the bromide ion.

WARNINGS: PAVULON SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS, WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION.

In patients who are known to have myasthenia gravis small doses of Pavulon may have profound effects. A peripheral nerve stimulator is especially valuable in assessing the effects of Pavulon in such patients.



USAGE IN PREGNANCY: The safe use of pancuronium bromide has not been established with respect to the possible adverse effects upon fetal development. Therefore, it should not be used in women of childbearing potential and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the unknown hazards.

Pavulon may be used in operative obstetrics (Cesarean section), but reversal of pancuronium may be unsatisfactory in patients receiving magnesium sulfate for toxemia of pregnancy, because magnesium salts enhance neuromuscular blockade. Dosage should usually be reduced, as indicated, in such cases.

PRECAUTIONS: Although Pavulon has been used successfully in many patients with pre-existing pulmonary, hepatic, or renal disease, caution should be exercised in these situations. This is particularly true of renal disease since a major portion of administered Pavulon is excreted unchanged in the urine.

ADVERSE REACTIONS: Neuromuscular: the most frequently noted adverse reactions consist primarily of an extension of the drug's pharmacological actions beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle relaxation resulting in respiratory insufficiency or apnea. Inadequate reversal of the neuromuscular blockade by anticholinesterase agents has also been observed with Pavulon (pancuronium bromide) as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate.

Cardiovascular: A slight increase in pulse rate is frequently noted.

Gastrointestinal: Salivation is sometimes noted during very light anesthesia, especially if no anticholinergic premedication is used.

Skin: An occasional transient rash is noted accompanying the use of Pavulon.

Respiratory: One case of wheezing, responding to deepening of the inhalational anesthetic, has been reported.

DRUG INTERACTION: The intensity of blockade and duration of action of Pavulon is increased in patients receiving potent volatile inhalational anesthetics such as halothane, diethyl ether, enflurane and methoxyflurane.

Prior administration of succinylcholine, such as that used for endotracheal intubation, enhances the relaxant effect of Pavulon and the duration of action. If succinylcholine is used before Pavulon, the administration of Pavulon should be delayed until the succinylcholine shows signs of wearing off.

DOSAGE AND ADMINISTRATION: Pavulon should be administered only by or under the supervision of experienced clinicians. DOSAGE MUST BE INDIVIDUALIZED IN EACH CASE. See package insert for suggested dosages.

CAUTION: Federal law prohibits dispensing without prescription.

HOW SUPPLIED:

2 ml. ampuls—2 mg./ml.—boxes of 25, NDC # 0052-0444-26
5 ml. ampuls—2 mg./ml.—boxes of 25, NDC # 0052-0444-25
10 ml. vials—1 mg./ml.—boxes of 25, NDC # 0052-0443-25

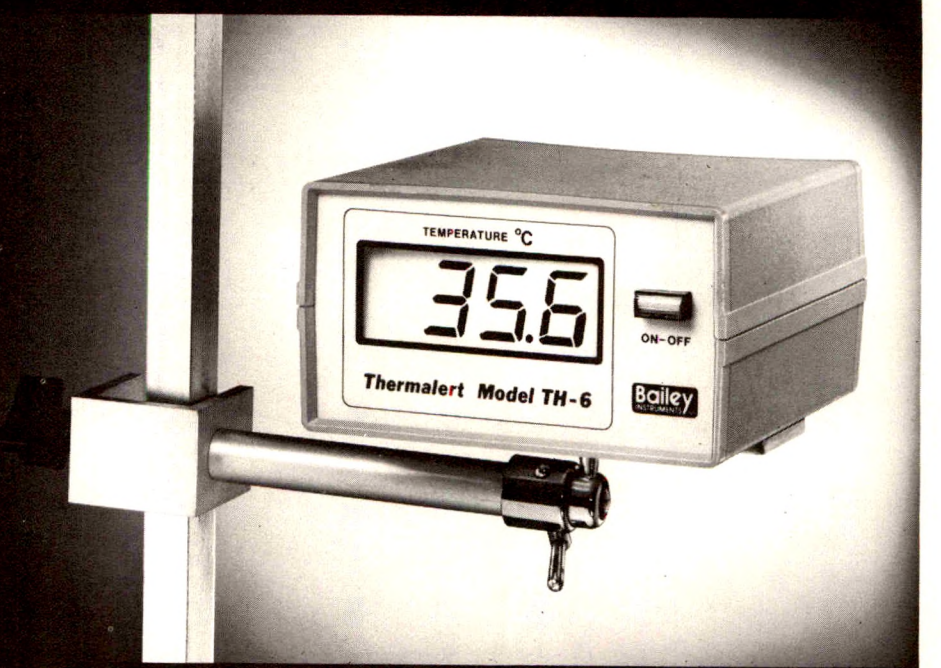
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Thermalert Monitoring Thermometers

- **DIGITAL DISPLAY**
  Gives 'early warning' of temperature changes.
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Model TH-6 Premium Monitor Thermometer with column clamp TH/CC-1

Thermalert thermometers are intended for continuous temperature monitoring in the OR and for use in specialized techniques such as hypothermic surgery. Thermalerts are as easy to use as glass thermometers, and much easier to read. They can indicate a patient's temperature in less than 20 seconds, which makes them ideal also for rapid screening of large groups such as blood donors.

These thermometers use Bailey type T interchangeable probes and sensors including our 'patient confortable' clinical types, needle probes and micro-probes. They also accept new disposable temperature-sensing stethoscope catheters such as those made by National Catheter Co.

Their digital display enhances reading accuracy and provides early warning of a temperature change, since a movement of 1/10th degree is immediately noticed. Thermalerts are the most advanced monitor thermometers so far devised.

Model TH-6 on Adjustable Stand TTS-1



SPECIFICATIONS

	TH-5	TH-6
Temperature Range:	25-45°C	0-50°C
Resolution:	0.1°C	0.1°C
Instrument Accuracy:	0.1°C ±1 digit	0.1°C ±1 digit
Calibration:	Conforms to National Bureau of Standards tables, Monograph 125	
Readout:	1/2" liquid crystal	1" liquid crystal
Battery Life:	700 hours continuous	1500 hours continuous

Use with Bailey Type T probes and microprobes (42 to choose from)

SAFETY FEATURES

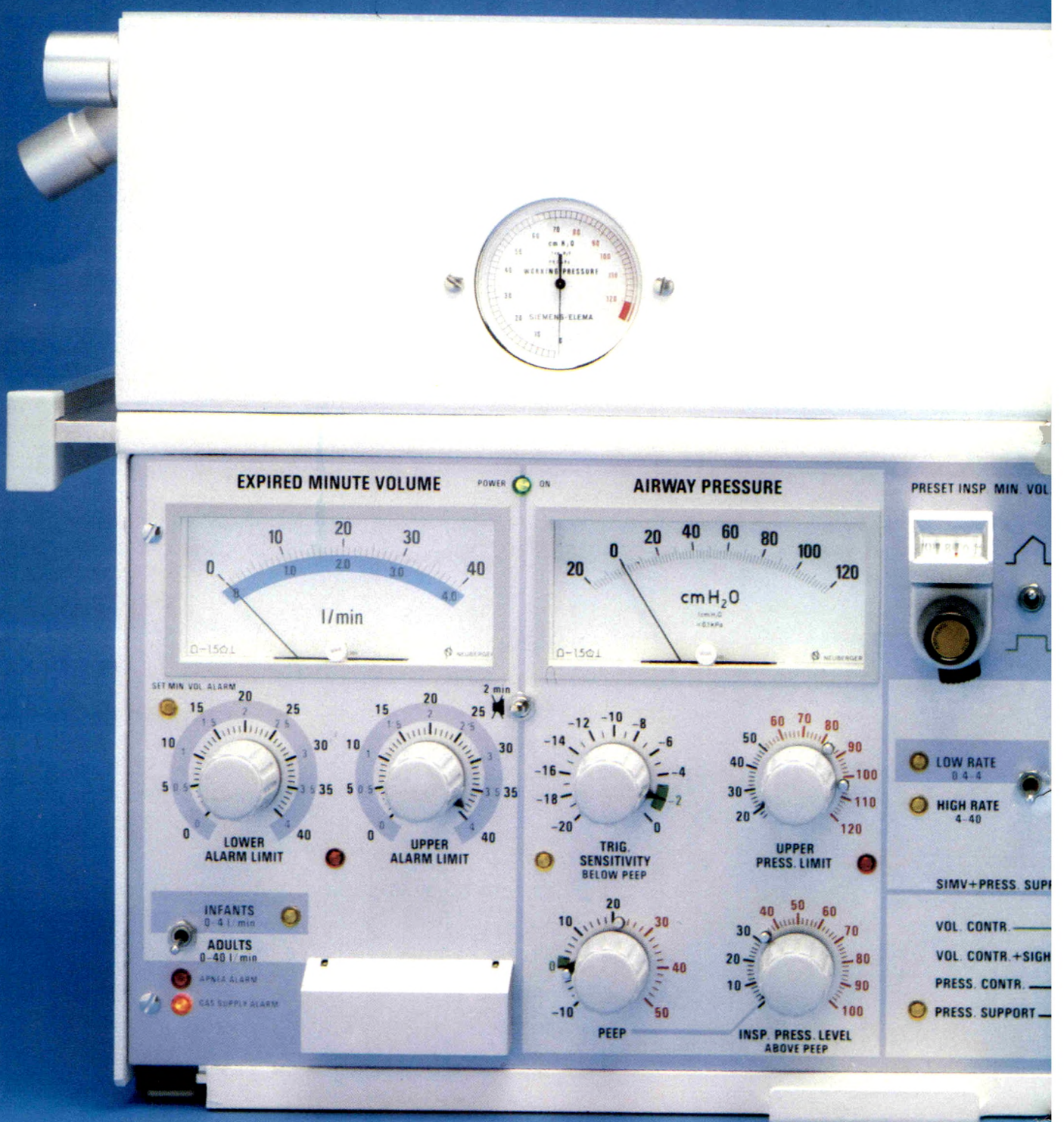
Test of Display: Automatic
Low Batteries: Automatic 2-stage warning
Faulty Probes: Automatic Warning
Case: High-insulating plastic
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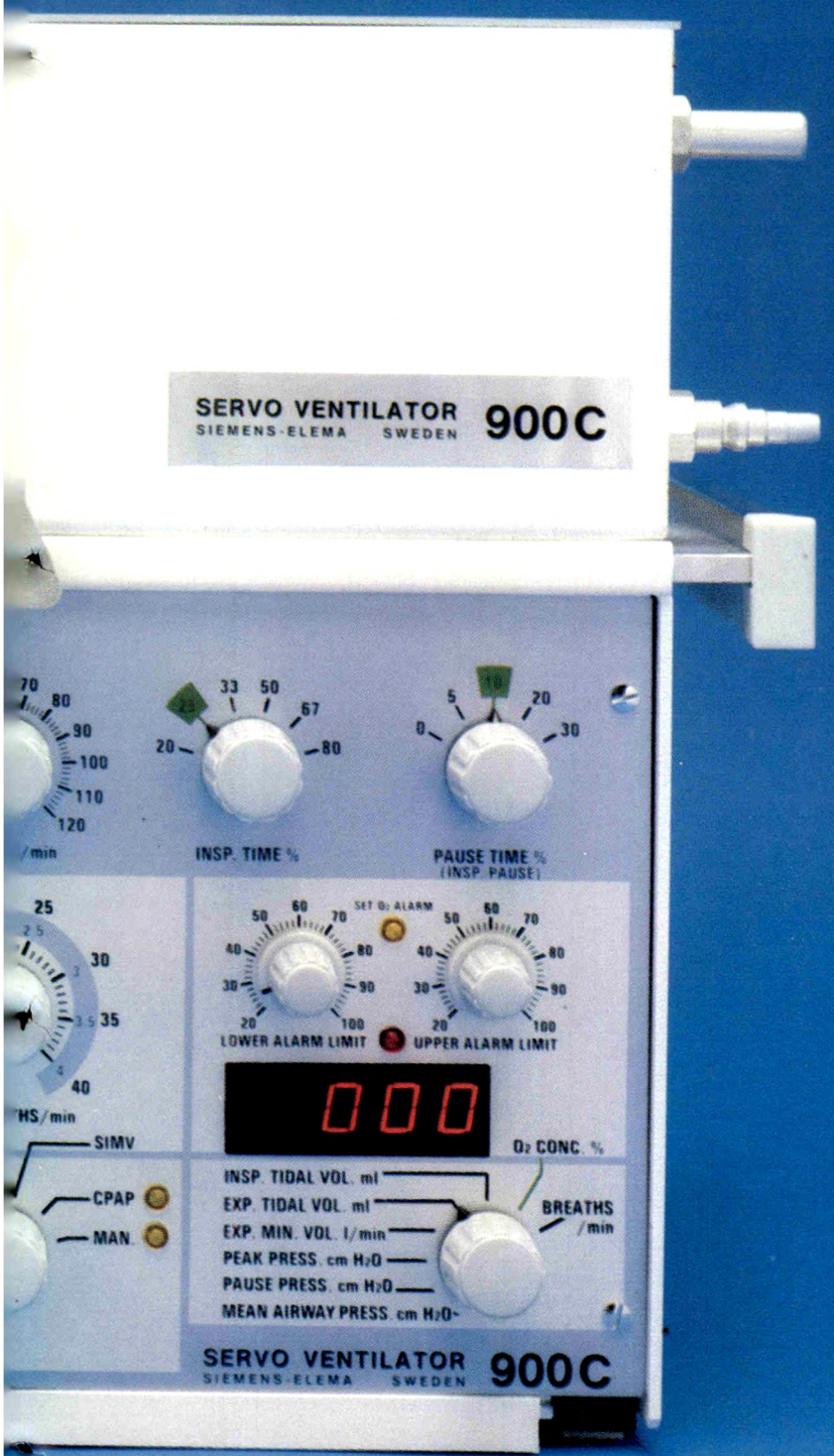
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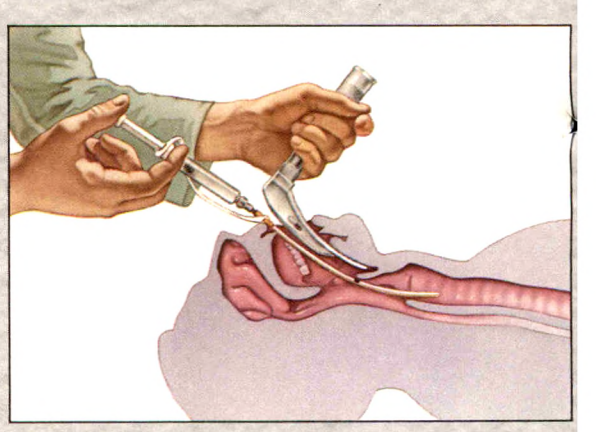
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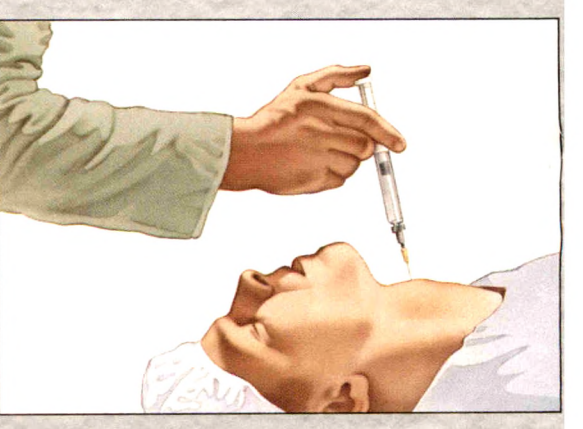
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REFERENCES

1. Bromage P: Concentrations of lidocaine in the blood after intravenous and endotracheal administration. *Anaesthesia*, 16:461, 1961.
2. Chu S: Plasma concentration of lidocaine after endotracheal spray. *Anesth. Analg.*, 54:438, 1975.
3. Pelton D: Plasma lidocaine concentrations following topical aerosol application to the trachea and bronchi. *Canad. Anaesth. Soc. J.*, 17:250, 1970.

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(Please see following page for a brief summary of prescribing information.)

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Before prescribing or administering, please consult complete product information, a summary of which follows:

CONTRAINDICATIONS: Lidocaine hydrochloride sterile solution is contraindicated in patients with a known history of hypersensitivity either to local anesthetics of the amide type or to other components of the sterile solution.

PRECAUTIONS: The safety and effectiveness of lidocaine hydrochloride depend on proper dosage, correct technique, adequate precautions, and readiness for emergencies. Standard textbooks should be consulted for specific techniques and precautions for various anesthetic procedures.

The lowest dosage that results in effective anesthesia should be used. Injection of repeated doses of lidocaine hydrochloride may cause significant increases in blood levels with each repeated dose due to slow accumulation of the drug or its metabolites. Tolerance varies with the status of the patient. Debilitated, elderly patients, acutely ill patients, and children should be given reduced doses commensurate with their age and physical status. Lidocaine hydrochloride should also be used with caution in patients with severe shock or heart block.

As with all injections of local anesthetics, retrobulbar injection should always be made slowly and with frequent aspirations.

Solutions to which a vasoconstrictor has been added should be used with caution in the presence of diseases which may adversely affect the patient's cardiovascular system. Serious cardiac arrhythmias may occur if preparations containing a vasoconstrictor are employed in patients during or following the administration of chloroform, halothane, cyclopropane, trichlorethylene, or other related agents.

Lidocaine hydrochloride should be used with caution in persons with known drug sensitivities. Patients allergic to para-aminobenzoic acid derivatives (procaine, tetracaine, benzocaine, etc.) have not shown cross sensitivity to lidocaine HCl.

Local anesthetics react with certain metals and cause the release of their respective ions which, if injected, may cause severe local irritation. Adequate precaution should be taken to avoid this type of interaction.

The safety of amide local anesthetics in patients with malignant hyperthermia has not been assessed, and therefore, those agents should be used with caution in such patients.

Drowsiness following lidocaine hydrochloride injection is *usually* an early indication of a high blood level of the drug and may occur following inadvertent intravascular administration or *rapid absorption* of lidocaine.

ADVERSE REACTIONS: Adverse reactions may result from high plasma levels due to excessive dosage, rapid absorption or inadvertent intravascular injection. Such reactions are systemic in nature and involve the central nervous system and/or the cardiovascular system. A small number of reactions may result from hypersensitivity, idiosyncrasy or diminished tolerance on the part of the patient.

CNS reactions are excitatory and/or depressant, and may be characterized by nervousness, dizziness, blurred vision and tremors, followed by drowsiness, convulsions, unconsciousness and possibly respiratory arrest. The excitatory reactions may be very brief or may not occur at all, in which case the first manifestations of toxicity may be drowsiness, merging into unconsciousness and respiratory arrest.

Toxic cardiovascular reactions to local anesthetics are usually depressant in nature and are characterized by hypotension, myocardial depression, bradycardia and possibly cardiac arrest.

Treatment of a patient with toxic manifestations consists of assuring and maintaining a patent airway, supporting ventilation with oxygen, and assisted or controlled ventilation (respiration) as required. This usually will be sufficient in the management of most reactions. Should a convulsion persist despite ventilation therapy, small increments of anticonvulsive agents may be given intravenously. Examples of such agents include benzodiazepine (e.g., diazepam), ultrashort acting barbiturates (e.g., thiopental or thiamylal) or a short acting barbiturate (e.g., pentobarbital or secobarbital). Cardiovascular depression may require circulatory assistance with intravenous fluids and/or vasopressors (e.g., ephedrine) as dictated by the clinical situation.

Allergic reactions may occur as a result of sensitivity either to local anesthetics or to other components of the sterile solution. Anaphylactoid type symptomatology and reactions, characterized by cutaneous lesions, urticaria, edema, should be managed by conventional means. The detection of potential sensitivity by skin testing is of limited value.

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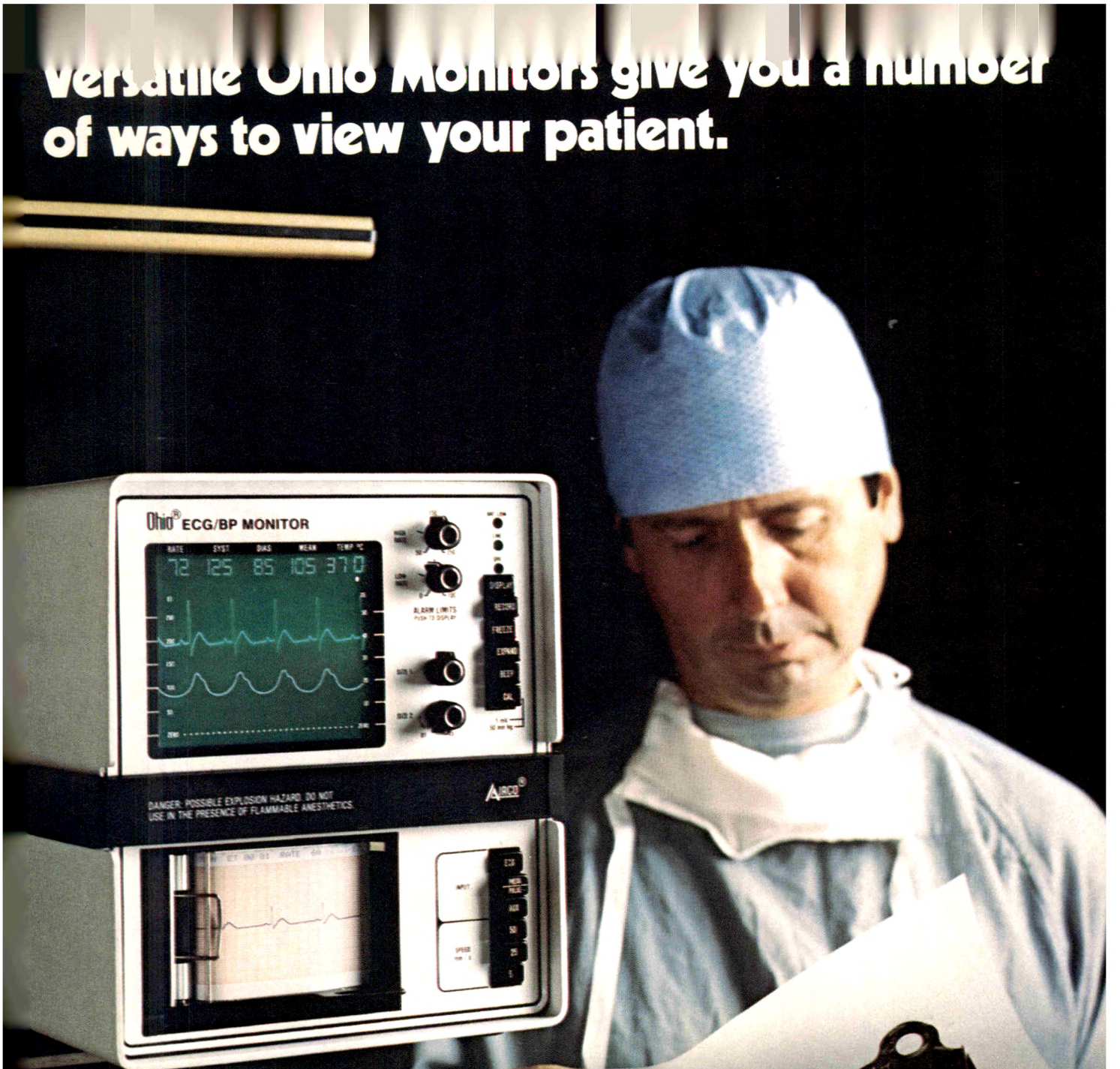
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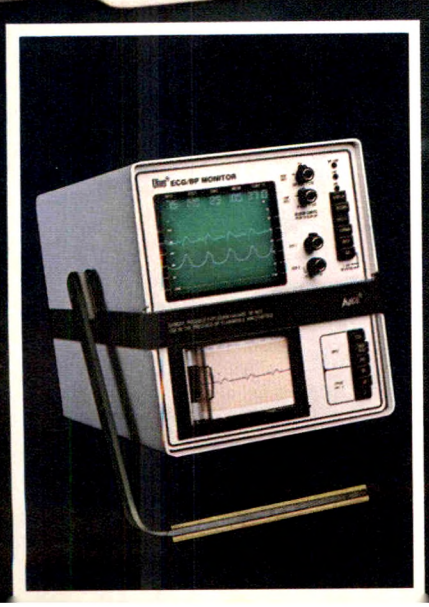
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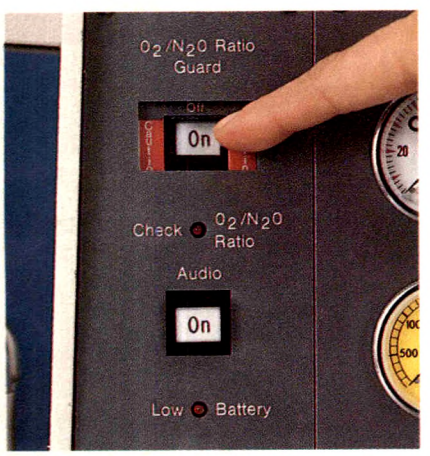
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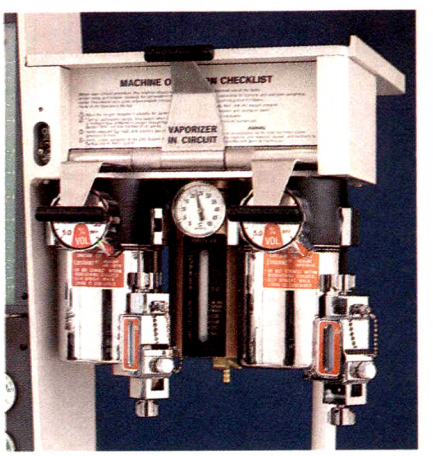
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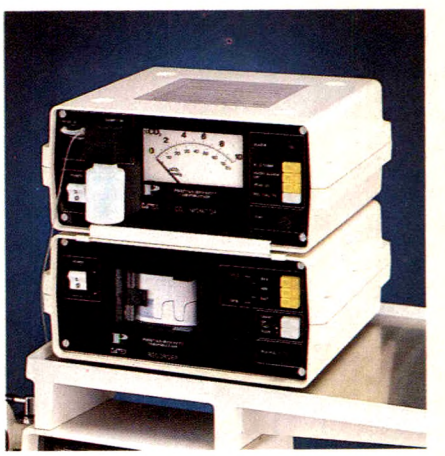
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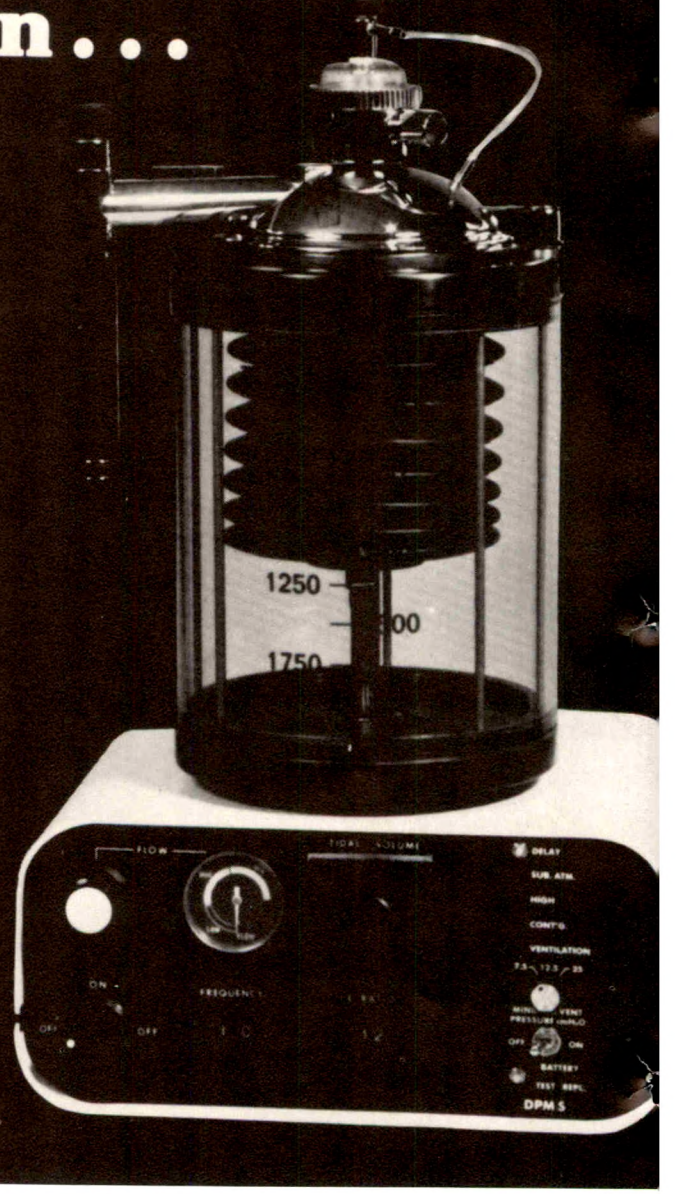
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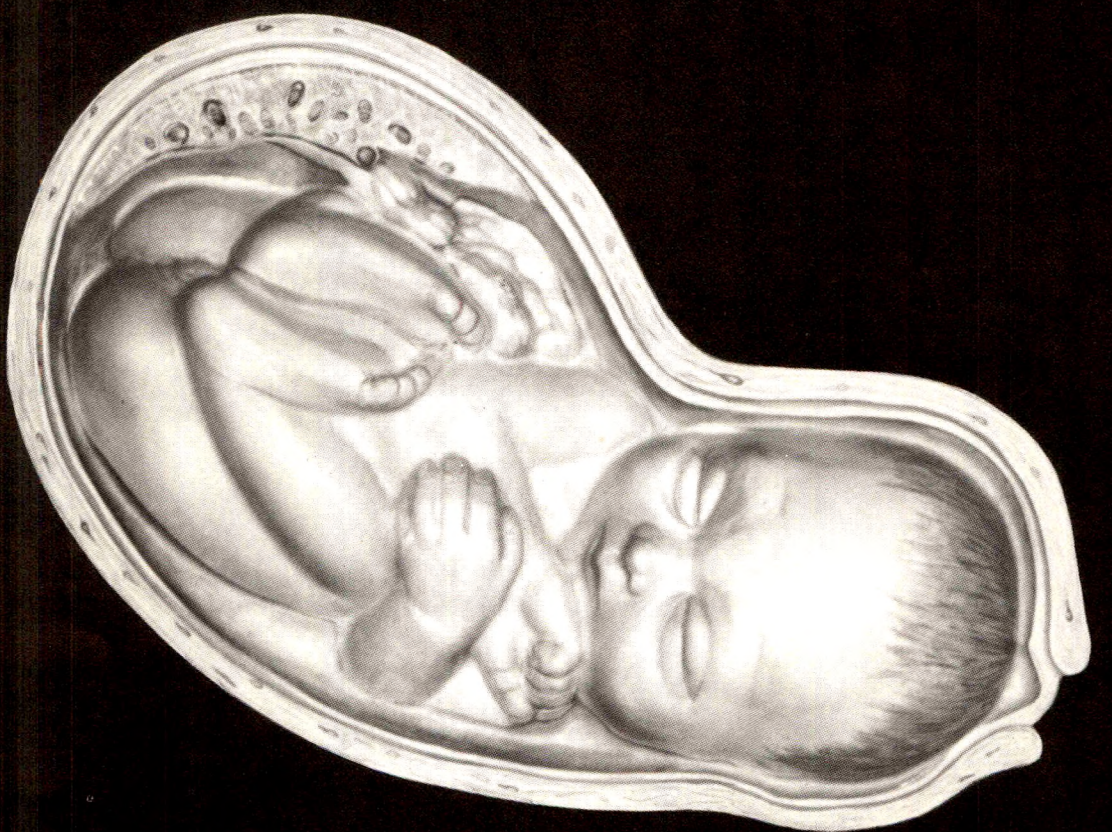
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Please consult full prescribing information before prescribing. A summary follows:

Indications. Peripheral nerve block, infiltration, sympathetic block, caudal, or epidural block.

Contraindication. Marcaine is contraindicated in patients with known hypersensitivity to it.

Warnings. RESUSCITATIVE EQUIPMENT AND DRUGS SHOULD BE READILY AVAILABLE WHEN ANY LOCAL ANESTHETIC IS USED.

Usage in Pregnancy. The relevance to the human is not known. Safe use in pregnant women other than those in labor has not been established.

Until further clinical experience is gained, paracervical block with Marcaine is not recommended. Fetal bradycardia frequently follows paracervical block with some amide-type local anesthetics and may be associated with fetal acidosis. Added risk appears to be present in prematurity, toxemia of pregnancy, and fetal distress.

The obstetrician is warned that severe persistent hypertension may occur after administration of certain oxytocic drugs, if vasopressors have already been used during labor (e.g., in the local anesthetic solution or to correct hypotension).

Solutions containing a vasoconstrictor, particularly epinephrine or norepinephrine, should be used with extreme caution in patients receiving monoamine oxidase (MAO) inhibitors or antidepressants of the triptyline or imipramine types, because severe, prolonged hypertension may result.

Local anesthetics which contain preservatives, i.e., those supplied in multiple dose vials, should not be used for caudal or epidural anesthesia.

Until further experience is gained in children younger than 12 years, administration of Marcaine in this age group is not recommended.

Precautions. The safety and effectiveness of local anesthetics depend upon proper dosage, correct technique, adequate precautions, and readiness for emergencies.

The lowest dosage that gives effective anesthesia should be used in order to avoid high plasma levels and serious systemic side effects. Injection of repeated doses of Marcaine may cause significant increase in blood levels with each additional dose, due to accumulation of the drug or its metabolites or due to slow metabolic degradation. Tolerance varies with the status of the patient. Debilitated, elderly patients and acutely ill patients should be given reduced doses commensurate with age and physical condition.

Solutions containing a vasoconstrictor should be used cautiously in areas with limited blood supply, in the presence of diseases that may adversely affect the patient's cardiovascular system, or in patients with peripheral vascular disease.

Marcaine should be used cautiously in persons with known drug allergies or sensitivities, particularly to the amide-type local anesthetics.

Serious dose-related cardiac arrhythmias may occur if preparations containing a vasoconstrictor such as epinephrine are employed in patients during or following the administration of chloroform, halothane, cyclopropane, trichloroethylene, or other related agents. In deciding whether to use these products concurrently in the same patient, the combined action of both agents upon the myocardium, the concentration and volume of vasoconstrictor used, and the time since injection, when applicable, should be taken into account.

Caution is advised in administration of repeat doses of Marcaine to patients with severe liver disease.

Use in Ophthalmic Surgery. When Marcaine 0.75% is used for retrobulbar block, complete corneal anesthesia usually precedes onset of clinically acceptable external ocular muscle akinesia. Therefore, presence of akinesia rather than anesthesia alone should determine readiness of the patient for surgery.

Adverse Reactions. Reactions to Marcaine are characteristic of those associated with other amide-type local anesthetics. A major cause of adverse reactions to this group of drugs is excessive plasma levels, which may be due to overdosage, inadvertent intravascular injection, or slow metabolic degradation.

Excessive plasma levels of the amide-type local anesthetics cause systemic reactions involving the central nervous system and the cardiovascular system. The *central nervous system effects* are characterized by excitation or depression. The first manifestation may be nervousness, dizziness, blurred vision, or tremors, followed by drowsiness, convulsions, unconsciousness, and possibly respiratory arrest. Since excitement may be transient or absent, the first manifestation may be drowsiness, sometimes merging into unconsciousness and respiratory arrest. Other central nervous system effects may be nausea, vomiting, chills, constriction of the pupils, or tinnitus. The *cardiovascular manifestations* of excessive plasma levels may include depression of the myocardium, blood pressure changes (usually hypotension), and cardiac arrest. In obstetrics, cases of fetal bradycardia have occurred (see Warnings). *Allergic reactions*, which may be due to hypersensitivity, idiosyncrasy, or diminished tolerance, are characterized by cutaneous lesions (e.g., urticaria), edema, and other manifestations of allergy. Detection of sensitivity by skin testing is of doubtful value. Sensitivity to methylparaben preservatives added to multiple dose vials has been reported. Single dose vials without methylparaben are also available.

Reactions following epidural or caudal anesthesia also may include: high or total spinal block; urinary retention; fecal incontinence; loss of perineal sensation and sexual function; persistent analgesia, paresthesia, and paralysis of the lower extremities; headache and backache; and slowing of labor and increased incidence of forceps delivery.

Treatment of Reactions. Toxic effects of local anesthetics require symptomatic treatment; there is no specific cure. The physician should be prepared to maintain an airway and to support ventilation with oxygen and assisted or controlled respiration as required. Supportive treatment of the cardiovascular system includes intravenous fluids and, when appropriate, vasopressors (preferably those that stimulate the myocardium). Convulsions may be controlled with oxygen and intravenous administration, in small increments, of a barbiturate, as follows: preferably, an ultrashort-acting barbiturate such as thiopental or thiamylal; if this is not available, a short-acting barbiturate (e.g., secobarbital or pentobarbital) or diazepam. Intravenous barbiturates or anticonvulsant agents should only be administered by those familiar with their use.

Composition of Solutions.

Marcaine 0.25% — Each ml contains 2.5 mg bupivacaine with NaCl for isotonicity in water for injection.

Marcaine 0.5% — Each ml contains 5 mg bupivacaine with NaCl for isotonicity in water for injection.

Marcaine 0.75% — Each ml contains 7.5 mg bupivacaine with NaCl for isotonicity in water for injection.

In multiple dose vials, each ml also contains 1 mg methylparaben.

In epinephrine, each ml also contains 0.0091 mg epinephrine bitartrate, 0.5 mg sodium bisulfite, 0.001 ml monothioglycerol, 2 mg ascorbic acid, 0.0017 ml 60% sodium lactate, and 0.1 mg edetate calcium disodium.

References:

1. Scanlon JW: Obstetric anesthesia as a neonatal risk factor in normal labor and delivery. *Clinics in Perinatology* 1:465-482, 1974.
2. Scanlon JW, Ostheimer GW, Brown WU, et al: Neurobehavioral responses and drug concentrations in newborns after maternal epidural anesthesia with bupivacaine. *Anesthesiology* 45:400-405, 1976.
3. Ostheimer GW: Obstetrics and local anesthetics: Implications for the fetus and newborn. *Anesthesiology Review* 4:17-23, June 1977.

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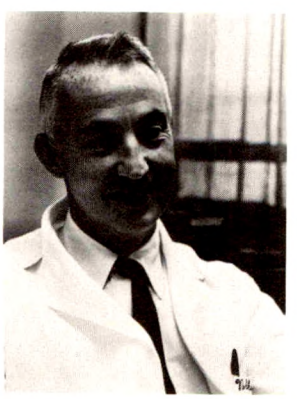
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I.A.R.S. 56th CONGRESS DISTINGUISHED LECTURERS

SEVENTEENTH ANNUAL BECTON, DICKINSON AND COMPANY OSCAR SCHWIDETZKY MEMORIAL LECTURE

Monday, March 15, 1982

"Heart and Heart-Lung Transplantation: The Stanford Experience"



Norman E. Shumway, M.D., Ph.D.

Frances and Charles D. Field Professor

and

Chairman, Department of Cardiovascular Surgery
Stanford University

Stanford, California

Dr. Shumway is widely known for his pioneering work in the field of open heart surgery, correction of congenital heart defects in children and heart transplantation. In 1981 he and his associates at Stanford initiated a new era in organ transplantation with completion of the first successful heart-lung transplant.

TWENTIETH ANNUAL BAXTER/TRAVENOL LECTURE

Tuesday, March 16, 1982

"Trials and Triumphs of a Presidents' Physician"



William M. Lukash, M.D.

Rear Admiral, Medical Corps., U.S. Navy (Ret.)

San Diego, California

Dr. Lukash served as White House physician during the terms of Presidents Johnson and Nixon, and as personal physician to Presidents Ford and Carter. He is now affiliated with the Division of Gastroenterology at the Scripps Clinic and Research Foundation in La Jolla, California.

EDITORIAL

Further Light on the Potencies of Local Anesthetics

OIL/WATER partition coefficients are commonly used as indices of the potencies of anesthetics. In the case of inhalation anesthetics oil/water partition coefficients can be determined in a relatively straightforward manner as these types of anesthetics are not subject to protonation or dissociation in biologic media. The resulting relationship between lipid solubility and potency is so linear that, knowing either of these two factors, one can with considerable confidence predict the other, a fact known for almost a century and a fact used to explain distribution of inhalation anesthetics in neuronal tissue and perhaps even their mode of action in nerve membranes. The same is not true for local anesthetics. Local anesthetics commonly used in clinical practice are both protonated and dissociated into charged and uncharged forms in biologic fluids at physiologic levels of pH. Anesthetic potencies of local anesthetics depend, therefore, not only upon the oil/water partition coefficients of uncharged molecules, but also on the partition coefficients of charged forms of local anesthetics. Furthermore, it is usually assumed in discussions of the distribution and mode of action of local anesthetics that the dissociation constant, the pKa, of local anesthetics is the same in lipid media as it is in aqueous media. Whether this assumption is, or is not, valid has not been adequately addressed, yet it is critical to our understanding of the mode of action of local anesthetics. As a result, the relationship between lipid solubility and anesthetic potency of local anesthetics is not as clear-cut, linear, predictable, or even accurately determined as it is in the case of inhalation anesthetics.

In the present issue Ueda and associates (p 56) evaluate some of the factors involved in determining the distribution of local anesthetics between aqueous media and lipids. They also address the problem of the forms in which local anesthetics exist in lipid media. Their paper may understandably strike some readers as being an arcane exercise in physical chemistry which is neither relevant to nor intelligible to clinical anesthesiologists. Unintelligible as it may well be in certain of its details to the majority of us who are not versed in physical chemistry, the results are certainly germane to anyone who would aspire to complete understanding of where and how local anesthetics act and what factors govern their concentrations at their sites of action in pharmacologically active forms and pharmacologically active amounts.

The results of this seminal contribution by Ueda and co-workers include demonstration that the coefficient of distribution of local anesthetics in water and in lipids as usually measured represents an apparent partition coefficient, not a true coefficient of distribution which takes into account the form in which the local anesthetic exists in both aqueous and lipid phases. Furthermore, the data emphasize the fact that calculated values of partition coefficients depend in part upon whether concentrations of local anesthetics are given in terms of molarity, molality, or mole fraction. Partition coefficients also depend upon the lipid (oil) solvent employed in such studies, a frequently overlooked matter of substantial importance when attempting to evaluate events that transpire where things count most, i.e., at their site of action in lipid layers of nerve membranes. The possibility that partition coefficients of local anesthetics (and inhalation anesthetics, too, for that matter) may vary in neuronal structures depending on the type of lipid present poses major problems in our understanding of the site of action and the mode of action of anesthetics. Finally, the data of Ueda et al demonstrate that dissociation constants of local anesthetics are lower in lipids than in aqueous media, an observation which implies that in lipid media there will be a relative increase in uncharged forms of local anesthetics over charged forms. This in turn alters our understanding of the relationship between oil/water partition coefficients of local anesthetics and their potency since although it is in the uncharged form that local anesthetics cross biologic barriers, including cell membranes, it is generally agreed that it is in the charged form that they act on nerve membrane function.

The paper by Ueda et al emphasizes the complexities of accurate determinations of oil/water partition

coefficients of local anesthetics. In so doing it provides us with a basis for understanding why and how partition coefficients of local anesthetics as determined in the past have not provided calculations of anesthetic potencies of local anesthetics with the same accuracy as they have in the case of potent inhalation anesthetics. Application of the data and principles elucidated by Ueda and co-workers to future studies will do much to increase our understanding both of the relative potencies of local anesthetics, as well as their sites and modes of action. The end result will be better clinical local anesthetics and a better selection and use of them.

Nicholas M. Greene, MD
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ANESTH ANALG
1982;61:3-9

Cardiovascular Effects of Convulsant and Supraconvulsant Doses of Amide Local Anesthetics

Rudolph H. de Jong, MD,* Robert A. Ronfeld, PhD,† and Richard A. DeRosa, PhD‡

DE JONG, R. H., RONFIELD, R. A., AND DEROSA, R. A.: Cardiovascular effects of convulsant and supraconvulsant doses of amide local anesthetics. Anesth Analg 1982;61:3-9.

Because resuscitation from toxic responses to bupivacaine (B) or etidocaine (E) is said to be difficult, the cardiovascular effects of these two local anesthetics were compared with those of lidocaine (L) in 40 lightly anesthetized, ventilated cats. First, the circulatory effects of a threshold convulsant dose (1 × CD) of local anesthetic were determined. One hour later, local anesthetic was infused beyond the onset of convulsions until the blood pressure (BP) decreased to less than 50 torr, or until the electroencephalogram (EEG) became flat. When drugs were infused at equiconvulsant rates (1 mg/kg/min for B and E; 4 mg/kg/min for L), electrical convulsions began after 4 to 6 minutes. Nodal and ventricular cardiac arrhythmias regularly appeared with B and E, but not with L. BP increased with B and E, but decreased slightly with L. B and E seizures lasted approximately 2 times longer than L seizures; BP and electrocardiogram (ECG) returned to control levels within 10 minutes. After full recovery, local anesthetic infusion was restarted; all cats survived at least 2 × CD. Arrhythmias reappeared after approximately 0.6 × CD of B or E. Only eight of 15 cats had arrhythmias after 2 × CD of L. After the onset of seizures, BP decreased progressively with B or E, more rapidly with L. When BP reached 50% of control levels after 2.3 × CD of L, 12 cats were given ephedrine, 1 mg, and survived 3 × CD of L; of the other three cats, two died before 3 × CD of L. Cats given B or E did not require ephedrine, and eight of nine B and 13 of 15 E cats recovered after 3 × CD. It is concluded that cats survive at least 2 times the convulsant dose of amide local anesthetics, provided oxygenation and ventilation are supported. With higher doses, cardiac arrhythmias and hypotension increasingly compromise circulation.

Key Words: ANESTHETICS, Local: bupivacaine, etidocaine, lidocaine; TOXICITY: local anesthetics.

RESUSCITATION from sudden circulatory collapse following mishaps with bupivacaine or etidocaine is said to be difficult. Albright (1), for instance, collected six incidents of cardiovascular collapse from rapid injection of these local anesthetics and deplored the " . . . paucity of experimental or clinical data delineating the effects of bupivacaine and etidocaine on the cardiovascular system above the convulsive threshold."

We studied the cardiovascular effects of threshold convulsant as well as supraconvulsant doses of bupivacaine and etidocaine in ventilated cats, and compared them with lidocaine. Lethality of these local anesthetics was evaluated by giving more than 3 times the convulsant dose. Our results show that cats can survive at least 2 times the convulsant dose of amide local anesthetics, provided they are adequately ventilated and oxygenated, and 3 times the convulsant dose of hypotension is corrected with a vasopressor such as ephedrine.

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Supported in part by a research grant from Breon Laboratories.

Received from the Anesthesia Research Laboratories, Tufts University School of Medicine, Boston, and Astra Pharmaceutical Products, Worcester, Massachusetts. Accepted for publication September 1, 1981.

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Methods

Forty adult cats with a mean weight of 3.7 kg (range 3.2 to 4.8 kg) were anesthetized with nitrous oxide, halothane, and oxygen, then intubated under direct vision. Percentage of CO_2 at the tip of the endotracheal tube was monitored continuously with a digital infrared analyzer. Esophageal temperature was kept at 37.5 ± 0.5°C with circulating warm water blankets. Electrocardiogram (ECG) electrodes were inserted in the four limbs, and venous and arterial catheters placed in the right femoral vessels. Another catheter was placed in the left femoral vein for fluid replace-

ment with 5% glucose in lactated Ringer's solution, given at 5 to 7 ml/kg/hr. Urine output was monitored with a bladder catheter. Gallamine (an agent commonly used by neuroscientists), 20 mg, was given and mechanical ventilation was started to maintain $P_{A_{CO_2}}$ at approximately 4.4% and $P_{a_{CO_2}}$ at 31 ± 2 torr; arterial blood pH was corrected to 7.42 with sodium bicarbonate 0.5 meq/kg if needed. A midline scalp incision exposed the skull for placement of paired extradural electroencephalogram (EEG) electrodes in the frontal, temporal, and occipital regions of the cortex.

With surgical preparation finished, halothane was turned off, and ventilation continued for 1 hour with 70% nitrous oxide and oxygen. During this period, the EEG electrode leads were arranged in eight montages and recorded on a polygraph along with arterial blood pressure (BP), and ECG leads I, II, and III. Finally, nitrous oxide was replaced with oxygen-enriched air (mean arterial P_{O_2} 150 torr) and control records taken. ECG lead II, BP, and four EEG channels were recorded in parallel on magnetic tape for permanent storage.

After control records, the threshold convulsant dose of local anesthetic was determined by infusing lidocaine (4 mg/kg/min, n = 15), bupivacaine (1 mg/kg/min, n = 10), or etidocaine (1 mg/kg/min, n = 15) with a Harvard pump until the onset of high voltage epileptiform seizure bursts in all EEG leads. Arterial samples were drawn intermittently for measurement of blood gases and pH, and for assay of local anesthetic plasma levels (using a gas chromatograph with a nitrogen-selective detector). After the postictal EEG changes had waned, gallamine, 20 mg, was repeated and nitrous oxide 70% with oxygen was restarted.

One hour later, nitrous oxide was replaced with oxygen-enriched air. The local anesthetic was reinfused at the same rate until either 3 times the threshold convulsant dose (CD) had been given, the EEG became isoelectric, or the BP decreased to less than 50 torr. In seven cats surviving 3 times the CD of bupivacaine or etidocaine, infusion was continued until circulatory failure ensued. As BP was consistently lower with lidocaine, 12 cats in that group received ephedrine, 1 mg, to evaluate the effect of blood pressure elevation on circulation and EEG.

Averaged results were computed as absolute values or as percentages of initial state, expressed as mean and standard deviation. Differences between values were evaluated for significance by *t*-test at the 95% probability level.

Results

Blood Pressure

Control systolic blood pressures (BP) did not differ significantly between the three groups of cats (Table 1). During infusion of a threshold convulsant dose of local anesthetic, the systolic BP in cats given lidocaine decreased to a mean 5% less than control levels at the end of infusion, whereas the BP during infusion of bupivacaine and etidocaine increased steadily and significantly to approximately 15% greater than control levels (Fig 1). One minute following the end of infusion, with convulsions at full intensity, arterial pressures in all cats were elevated significantly by at least 10% greater than control levels. BP soon returned to control levels after seizures stopped spontaneously.

BP still was at control levels when local anesthetic infusion was restarted 1 hour later. At first, mean systolic BP took a course similar to that described above for a threshold convulsant dose (Fig 1). Throughout, mean systolic BP was lower during lidocaine infusion than during infusions of bupivacaine or etidocaine. After 2 times the convulsant dose (2 × CD) all pressures were significantly less than control levels, and decreased progressively as more drug was given. (BP at 3 × CD of lidocaine is not shown in Fig 1 because these animals had received a vasopressor.)

In the first two cats given lidocaine, BP decreased to less than 30 torr and circulation failed after 2.5 × CD. Seeing that trend, we restored BP in the remaining cats if it decreased to less than 50% of control

TABLE 1
Systolic Blood Pressure (BP) and Heart Rate*

	n	Initial control levels		1 hr after convulsions	
		Systolic BP	Heart rate	Systolic BP	Heart rate
		torr	*beats/min*	*torr*	*beats/min*
Lidocaine	15	136 ± 20	247 ± 18	134 ± 20	245 ± 24
Bupivacaine	10	151 ± 12	251 ± 21	159 ± 20†	259 ± 41
Etidocaine	15	140 ± 19	233 ± 32	136 ± 18	233 ± 40

* Values are means ± SD.
† n = 9.

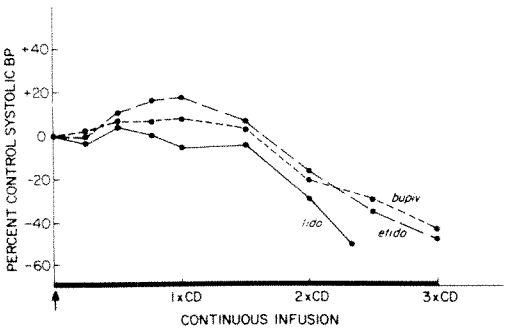


FIG 1. Mean systolic blood pressure (% control) during infusion of etidocaine (etido), bupivacaine (bupiv), or lidocaine (lido). Convulsions started at threshold convulsant dose (1 × CD) and continued thereafter. After 2.3 × CD of lidocaine, BP was half control levels and EEG had flattened; BP restored with ephedrine at that time (not shown).

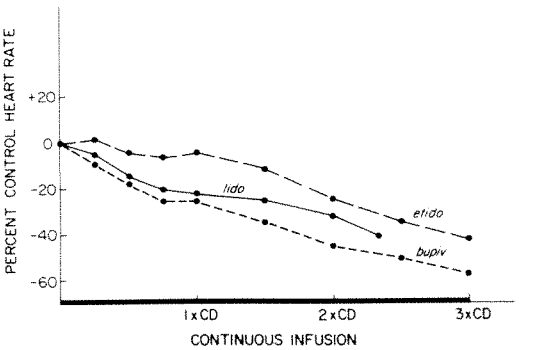


FIG 2. Mean heart rate (% control) during infusion of up to 3 times convulsant dose (3 × CD) of amide local anesthetics. Convulsions started at 1 × CD and continued thereafter. Note steady downward trend in heart rate, which was also seen during initial infusion of threshold convulsant dose. After 2.3 × CD of lidocaine, ephedrine was given to restore BP and EEG (subsequent increase in heart rate is not shown).

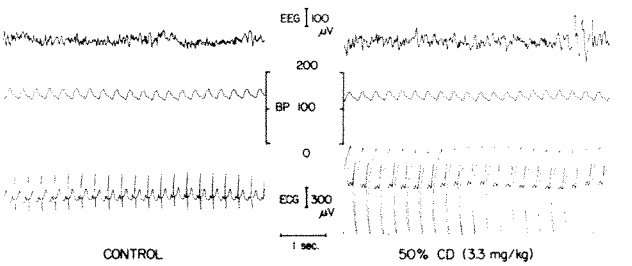


FIG 3. Here and in Figs 4 to 8, left temporal-occipital EEG (top), femoral arterial BP (center), and lead II ECG (bottom), with control tracings (left). Etidocaine, 1 mg/kg/min, was given. In right frame, note appearance of preseizure slow wave EEG cluster at far right, and increase in amplitude and width of QRS complexes after 0.5 × CD of etidocaine.

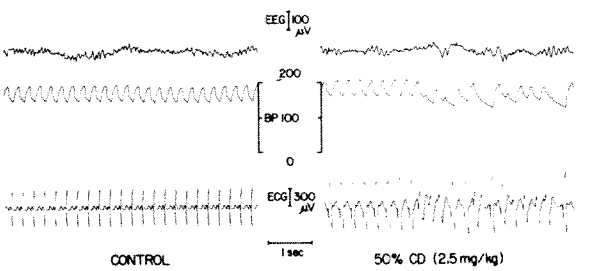


FIG 4. As in Fig 3 except that bupivacaine, 1 mg/kg/min, was given. After 0.5 × CD, slow waves begin to dominate EEG, and arterial pulse is irregular; basic cardiac rhythm is nodal with ventricular ectopic beats.

levels—12 of 13 cats required ephedrine after an average 2.3 × CD of lidocaine. In the remaining cat, BP was 65% of control levels after 3 × CD of lidocaine. The BP in the ephedrine-treated cats was only 4% less than control levels after 3 × CD of lidocaine, and was 24% greater than control levels 10 minutes later.

The mean systolic BP was 71% of control levels after 2.5 × CD of bupivacaine. In one cat with severe arrhythmias, circulation failed with further infusion of bupivacaine. The mean systolic BP was 65% of control levels after 2.5 × CD of etidocaine. In two cats with severe arrhythmias, circulation failed with further infusion of etidocaine. Five minutes after 3 × CD of etidocaine, the mean BP was 93% of control levels in the nine cats not given additional drug.

Heart Rate

Control heart rates did not differ significantly between groups. Heart rates had also returned to control levels before local anesthetic was reinfused 1 hour after determining the threshold convulsant dose (Table 1). The heart rate followed a steady downward course during infusion (Fig 2); it was significantly slower than control heart rates after 0.5 × CD of bupivacaine or lidocaine, and after 1.5 × CD of etidocaine. The heart slowed most with bupivacaine, and least with etidocaine. Heart rate during infusion of 3 × CD of lidocaine is not shown in Fig 2 because these animals had received ephedrine to elevate the BP.

Electrocardiogram

With bupivacaine and etidocaine, QRS complexes began to widen and increase in amplitude within 1 minute (1 mg/kg) of infusion. After approximately half the convulsant dose (0.5 × CD) of either drug, the QRS amplitude was 2 to 4 times greater than control levels in lead II (Fig 3). Increasing numbers of ectopic ventricular beats appeared as infusion progressed (Fig 4). The ECG during infusion of 0.5 × CD of lidocaine, conversely, remained essentially unchanged from control tracings (except for the above-mentioned slowing of heart rate) as seen in Fig 5.

Recovery of the ECG to sinus pattern after a threshold convulsant dose usually occurred shortly after seizures ended, and always within 10 minutes.

Identical ECG changes reappeared when local anesthetic was infused the second time. In cats given bupivacaine and etidocaine, aberrant intraventricular conduction and nodal and ventricular arrhythmias predominated, usually in the form of coupled beats (Fig 6), but with an idioventricular rhythm in five cats (Fig 7). All bupivacaine-treated cats had arrhythmias by the time seizures started, with increasing shift to ventricular beats as infusion continued to 3 × CD or more.

Of the 15 etidocaine-treated cats, 12 had nodal or ventricular arrhythmias before the onset of seizures, arrhythmias that continued until 3 × CD or more had been given. Three cats maintained sinus rhythms throughout etidocaine infusion. P waves were identifiable longer in etidocaine-treated cats than in bupivacaine-treated cats, although the ventricular complexes soon assumed increasingly bizarre shapes, with intraventricular conduction defects resembling various bundle branch blocks. PVCs appeared in half the cats given etidocaine and in two cats bursts of ventricular tachycardia occurred.

In marked contrast, only one of 15 cats given lidocaine developed arrhythmias before the onset of convulsions. Seven cats remained in sinus rhythm throughout infusion of 3 × CD of lidocaine (Fig 8). The remaining seven cats developed arrhythmias only after more than 2 × CD of lidocaine had been given. As noted, ephedrine, 1 mg, had to be given to 12 cats after 2.3 × CD of lidocaine, on the average. Ephedrine not only restored BP, it also converted arrhythmias to sinus rhythm in five of seven cats.

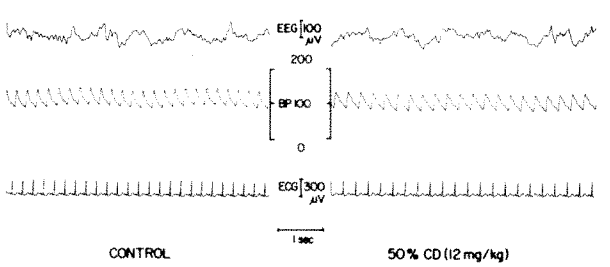


FIG 5. As in Fig 3 except that lidocaine, 4 mg/kg/min, was given at an equiconvulsant rate. After 0.5 × CD, slow waves dominate EEG; BP and ECG are essentially unchanged except for slowing of heart rate.

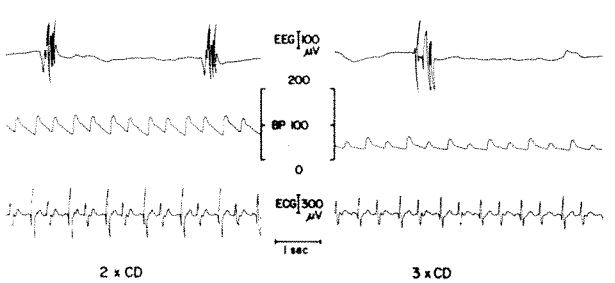


FIG 6. After 2 × CD (left) and 3 × CD (right) of bupivacaine (1 mg/kg/min), epileptiform bursts break out from EEG base line; interictal silent interval lengthens with increasing dose. BP, still well maintained by nodal bigeminy on left, has deteriorated on right.

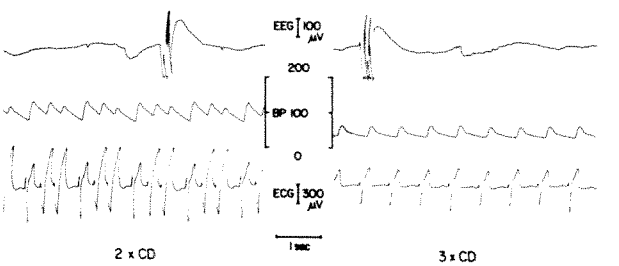


FIG 7. After 2 × CD (left) and 3 × CD (right) of etidocaine (1 mg/kg/min), epileptiform bursts, separated by interictal silence, dominate EEG. BP continues to decrease, and ECG changes from nodal rhythm with PVCs to idioventricular from left to right.

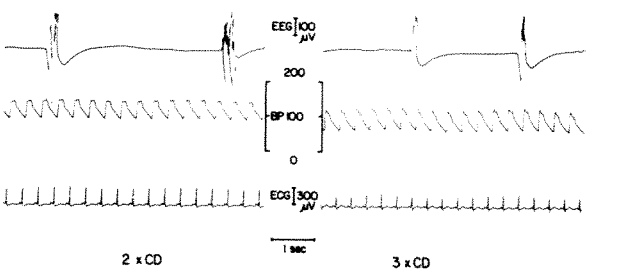


FIG 8. After 2 × CD (left) and 3 × CD (right) of lidocaine (4 mg/kg/min), epileptiform bursts break out from electrically silent EEG background; seizure bursts become briefer with increasing dose. On right, BP has been restored with ephedrine. Except for slowing, shortening of P-R interval and lowering of S-T segment, ECG has changed little from control tracings (Fig 5).

Survival

Two of the 15 cats given lidocaine died from circulatory failure after 2.5 × CD. Twelve of the remaining 13 cats infused with lidocaine were given ephedrine because of severe hypotension and isoelectric EEG. The vasopressor promptly restored BP and electrical convulsions, and all 13 survived 3 × CD of lidocaine. One cat died from circulatory failure after 2.7 × CD of bupivacaine; two cats died after 2.6 × CD and 2.8 × CD of etidocaine. The remaining eight cats given bupivacaine and 13 of the cats given etidocaine survived 3 × CD without ephedrine.

In seven animals, infusion was continued beyond 3 × CD. One cat survived 3.5 × CD of bupivacaine, two survived 4 × CD, and one reached 5 × CD of

bupivacaine although with a systolic BP of 25 torr. Although one cat died from 3.5 × CD of etidocaine, two other cats given 4 × CD and 4.5 × CD of etidocaine survived.

Seizure Doses and Plasma Levels

Although bupivacaine was the most potent convulsant, its seizure dose did not differ significantly from that of etidocaine, and both were approximately one fourth of the lidocaine dose (Table 2). As lidocaine was given 4 times more rapidly, time to onset of convulsions with the three drugs did not differ significantly (Table 2). Although the convulsant doses of bupivacaine and etidocaine were nearly identical, the former's plasma levels were approximately half those of the latter (Table 2). Bupivacaine and etidocaine convulsions lasted approximately twice as long as those produced by lidocaine. Nevertheless, the plasma drug level had decreased to the same extent (approximately 60% of peak) in each instance at the end of seizures (Table 2).

With the onset of seizures, the end-expired CO_2 increased (from 4.4% to 5.3% or more), requiring an increase in minute volume to compensate. By this means the arterial pH could be maintained close to 7.42 and the P_{CO_2} close to 31 (normal for cats); arterial P_{O_2} was consistently greater than 100 torr (mean value 151.3).

When local anesthetic administration was repeated after 1 hour, the convulsant doses were slightly less and onset times were slightly more rapid than the threshold values, but the differences were significant only for etidocaine (Table 2). Plasma levels of all three local anesthetics were still measurable when infusion was restarted (Table 3). Whereas lidocaine and bupivacaine values were only 10% to 15% of the peak level after 1 hour, the etidocaine level still was 35% of the peak level. Convulsant plasma levels during the second infusion were higher by at least 50% than when measured after giving the threshold convulsant doses.

Discussion

The experiment was performed in two stages so as to contrast the effects on the circulatory system of threshold convulsant doses with those of supraconvulsant doses of local anesthetics. Although some residual local anesthetic still was present at the start of the second phase, the convulsant dose was little reduced, and the cardiovascular responses to either convulsant dose were indistinguishable. The plasma concentration of local anesthetic at the onset of convulsions after reinfusion was much greater than after the initial determination, perhaps due in part to retained local anesthetic. However, we attribute the difference primarily to pharmacokinetic considerations. The first arterial sample was drawn at the onset of threshold convulsions when infusion had been

TABLE 2

Convulsant Doses (CD), Times to Onset of Convulsion, and Convulsant Plasma Levels of Local Anesthetics*

	n	Threshold CD	Time to onset of convulsions	Duration of convulsions	Plasma level		Repeat CD
					Start of seizures	End of seizures	
		mg/kg	*min*		*μg/ml*		*mg/kg*
Lidocaine	15	22.0 ± 4.4	5.5 ± 1.1	3.8 ± 1.3	19.6 ± 5.5	12.4 ± 1.9	20.4 ± 3.9
Bupivacaine	10	5.3 ± 2.1	5.3 ± 2.1	7.5 ± 2.9	3.6 ± 0.7	2.1 ± 1.1	4.6 ± 0.7†
Etidocaine	15	6.3 ± 1.2	6.3 ± 1.2	7.3 ± 2.9	6.6 ± 1.6	4.3 ± 0.9	5.3 ± 1.0‡

* Values are means ± SD.

† n = 9.

‡ Significantly different from threshold value.

TABLE 3

Plasma Concentrations (μg/ml) with Continuous Infusion*

	n	Start†	1 × CD	2 × CD	3 × CD
Lidocaine	15	2.6 ± 0.7	44.1 ± 9.5	67.7 ± 17.1	81.1 ± 29.4‡
Bupivacaine	9	0.7 ± 0.2	5.1 ± 1.6	9.9 ± 4.7	14.1 ± 2.8
Etidocaine	9	2.3 ± 1.0	12.0 ± 3.6	—	23.0 ± 6.5

* Values are means ± SD.

† One hour after a threshold convulsant dose.

‡ Blood pressure restored with ephedrine.

halted and the anesthetic plasma level had entered the steeply declining phase of drug distribution (2). The second arterial sample, conversely, was drawn during continuing infusion, with the plasma concentration curve in the rapidly ascending phase. This assumption seems reasonable in light of the work of Munson et al (3), who found little, if any, change in seizure threshold dose of plasma concentration after repeated administration of local anesthetics in monkeys.

To circumvent the respiratory depressant effects of local anesthetics (4) and the consequent effects of respiratory acidosis and hypoxia on the heart and on seizure threshold (5), we controlled ventilation. To do so effectively we used gallamine as a neuromuscular blocking agent because it is thought not to cross the blood-brain barrier. On the other hand, gallamine decreases potassium and sodium conductance in isolated nerve (6) and increases the seizure threshold to lidocaine in monkeys (7). To test the effect of gallamine on the seizure threshold in cats, we substituted metocurine in other experiments. Neither seizure threshold dose nor plasma level of bupivacaine differed significantly between the gallamine-treated cats and metocurine-treated cats (8).

We minimized lingering central nervous system (CNS) effects of general anesthesia for surgical preparation by using halothane. Afterwards, the animal was ventilated with nitrous oxide to eliminate halothane while maintaining light anesthesia under constant EEG surveillance. Although nitrous oxide was discontinued just before local anesthetic infusion, residual nitrous oxide might have elevated the seizure threshold to local anesthetic (9). We ventilated the animals with air and just enough oxygen to avoid hypoxia and its potential adverse effects on the heart and circulation, while at the same time avoiding the reduction in seizure threshold associated with inhalation of 100% oxygen (10).

Time to onset of seizures was approximately the same for bupivacaine or etidocaine given at a rate of 1 mg/kg/min as it was for lidocaine given at 4 mg/kg/min. Hence bupivacaine and etidocaine are approximately equally convulsant, and both are 4 times more potent convulsants than lidocaine in cats. These proportions are similar to those of others who found etidocaine to be as lethal as bupivacaine, and four times more lethal than lidocaine, when given as an intravenous bolus to mice (11). Also, the seizure threshold doses and plasma levels we observed in cats are comparable to those observed in monkeys (3).

Rate of infusion plays a role in establishing the convulsant dose. As the rate of etidocaine administration in monkeys was increased from 0.5 to 2.0 mg/kg/min, for instance, the total seizure dose decreased, whereas the effect of rate of infusion on the bupivacaine seizure dose was negligible (12). Similar observations were made in man, in whom bupivacaine was approximately twice as toxic as etidocaine when infused at 10 mg/min, but only 40% more toxic when infused at 20 mg/min (13). Whether these observations and ours reflect on conditions in man when local anesthetic is inadvertently injected into a blood vessel, we do not know.

We are unable to explain why bupivacaine and etidocaine (but not lidocaine) caused severe cardiac arrhythmias in our cats, especially since other investigators did not comment on the development of arrhythmias in different animal species. The monkeys in the study of Munson et al (3), for instance, were monitored by ECG during infusion of lidocaine, bupivacaine, or etidocaine and no arrhythmias were observed. In ventilated anesthetized dogs, likewise, no mention was made of ECG changes during infusion of bupivacaine or etidocaine (14). In other studies, in fact, bupivacaine and etidocaine protected the heart of dogs against epinephrine-induced arrhythmias (15). As the vagolytic action of gallamine increases heart rate and might have contributed to the generation of arrhythmias, we gave metocurine instead of gallamine before bupivacaine infusion in other experiments. Although the heart rate in cats given metocurine was some 16% slower than in those given gallamine, time of onset, incidence, and type of bupivacaine-induced arrhythmias were indistinguishable (8).

Further suggesting a specific arrhythmogenic action of bupivacaine and etidocaine is the fact that arrhythmias were not seen with subconvulsant doses of lidocaine. Recent in vitro studies of paced perfused rabbit hearts bear out the relatively milder cardiotoxic actions of lidocaine as against those of bupivacaine and etidocaine (16). Although all local anesthetics depress intracardiac impulse conduction and ventricular contractility in a concentration-related manner, less potent agents proved markedly less cardiodepressant than potent agents. To depress intraventricular conduction or prolong QRS duration by 50%, for instance, required a 10-fold or greater concentration of lidocaine than of bupivacaine or etidocaine. Seeing that we (and others) found only a 4-fold difference in convulsant threshold between these agents, the margin between cerebral and cardiac toxicity of lidocaine is at least 2.5 times wider with lidocaine than it is with bupivacaine or etidocaine. This certainly parallels our

in vivo observations; although speculative, it could be that the difficult cardiac resuscitation following bupivacaine or etidocaine mishaps in man (1) may be related to their greater potential for arrhythmogenicity, as demonstrated here.

That our animals survived the infusion of several-fold the convulsant dose of local anesthetics may be attributable to the aforementioned careful control of respiration, and fluid and acid-base balance. For, as shown in dogs paralyzed with pancuronium, ventilation prevents not only the acidemia, but also the hyperthermia seen during cocaine-induced convulsions, thereby permitting survival from normally lethal amounts of cocaine (17). In spontaneously breathing mice, by contrast, a convulsant dose of local anesthetic is close to a lethal dose (18). Indeed, Moore et al (19) have documented severe hypercarbia, hypoxia, and acidemia in several patients during bupivacaine-induced convulsions. Clearly, oxygenation and carbon dioxide elimination are vital to survival from supraconvulsant doses of local anesthetics. Whether pure alpha-adrenergic vasopressors would have been as effective as ephedrine, and whether ephedrine or another vasopressor would have enhanced survival after massive doses of bupivacaine or etidocaine remains to be seen.

We conclude that subconvulsant doses of bupivacaine and etidocaine can precipitate cardiac arrhythmias in cats, whereas lidocaine does not. Even so, well ventilated animals can survive at least twice the convulsant dose of any amide local anesthetic. Higher doses progressively decrease blood pressure; in the case of lidocaine, administration of a vasopressor such as ephedrine allows ventilated animals to survive 3 times or more the convulsant dose. Within the limits of extrapolation from cat to man, ventilation and support of circulation are vital elements in resuscitating patients given an overdose of local anesthetic.

ACKNOWLEDGMENTS

The technical assistance of John Bonin, Charles Gamble, and Jack Barkus is gratefully acknowledged. Plasma levels of bupivacaine were determined by Dr. Karabelas at the Massachusetts College of Pharmacy. The authors thank Astra Pharmaceutical for a complimentary supply of lidocaine and etidocaine, and Breon Laboratories for that of bupivacaine.

REFERENCES

1. Albright GA. Cardiac arrest following regional anesthesia with etidocaine or bupivacaine. Anesthesiology 1979;51:285–7.
2. Tucker GT, Mather LE. Pharmacokinetics of local anaesthetic agents. Br J Anaesth 1975;47:213–24.
3. Munson ES, Tucker WK, Ausinsch B, Malagodi MH. Etidocaine, bupivacaine and lidocaine seizure thresholds in monkeys. Anesthesiology 1975;42:471–8.
4. Daos FG, Lopez L, Virtue RW. Local anesthetic toxicity modified by oxygen and by combination of agents. Anesthesiology 1962;23:755–61.
5. Englesson S. The influence of acid-base changes on central nervous system toxicity of local anaesthetic agents. Acta Anaesth Scand 1974; 18:79–87.
6. Smith KJ, Schauf CL. Effects of gallamine triethiodide on membrane currents in amphibian and mammalian peripheral nerve. J Pharmacol Exp Ther 1981;217:719–26.
7. Munson ES, Wagman IH. Elevation of lidocaine seizure threshold by gallamine in rhesus monkeys. Arch Neurol 1973;28: 329–33.
8. de Jong RH, Gamble CA, Bonin JD. Neuromuscular blocking agents do not alter bupivacaine seizure threshold. Exp Neurol (in press 1982).
9. de Jong RH, Heavner JE, de Oliveira LF. Nitrous oxide elevates local anesthetic seizure threshold. Exp Neurol 1972;35:558–64.
10. Munson ES, Pugno PA, Wagman IH. Does oxygen protect against local anesthetic toxicity? Anesth Analg 1972;51:422–7.
11. Adams HJ, Kronberg GH, Takman BH. Local anesthetic activity and acute toxicity of etidocaine, a new long-acting agent. J Pharm Sci 1972;61:1829–31.
12. Malagodi MH, Munson ES, Embro WJ. Relation of etidocaine and bupivacaine toxicity to rate of infusion in rhesus monkeys. Br J Anaesth 1977;49:121–5.
13. Scott DB. Evaluation of the toxicity of local anaesthetic agents in man. Br J Anaesth 1975;47:56–61.
14. Liu P, Feldman H, Covino BG. Acute cardiovascular toxicity of lidocaine, bupivacaine and etidocaine in anesthetized ventilated dogs. Anesthesiology 1980;53:S231.
15. Chapin JC, Kushins LG, Munson ES, Schick LM. Lidocaine, bupivacaine, etidocaine, and epinephrine-induced arrhythmias during halothane anesthesia in dogs. Anesthesiology 1980;52: 23–6.
16. Block A, Covino BG. Effect of local anesthetic agents on cardiac conduction and contractility. Reg Anesth 1981;6:55–61.
17. Catravas JD, Waters ID. Acute cocaine intoxication in the conscious dog: studies on the mechanism of lethality. J Pharmacol Exp Ther 1981;217:350–6.
18. de Jong RH, Bonin JD. Deaths from local anesthetic-induced convulsions in mice. Anesth Analg 1980;59:401–5.
19. Moore DC, Crawford RD, Scurlock JE. Severe hypoxia and acidosis following local anesthetic-induced convulsions. Anesthesiology 1980;53:259–60.

ANESTH ANALG
1982;61:10-4

Treatment of Myocardial Ischemia with Halothane or Nitroprusside-Propranolol

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GERSON, J. I., HICKEY, R. F., AND BAINTON, C. R.: Treatment of myocardial ischemia with halothane or nitroprusside-propranolol. Anesth Analg 1982;61:10-4.

An experimental animal model was used to compare the effect of two drug interventions on myocardial ischemia. Elevation of the ST segment on epicardial electrocardiogram in response to temporary occlusion of the coronary artery was used as an index of ischemia. For multiple sites distal to the left-anterior descending coronary artery (LADCA), ST segments were obtained, measured, and totaled (ΣST). The effects of halothane (1.1% end-tidal concentration) were compared with those of a combination of nitroprusside and propranolol. The combination was given in a dosage that produced values for systemic blood pressure, heart rate, and maximal positive left-ventricular dP/dt (LV dP/dt) that were similar to those produced by halothane. Control measurements were obtained during chloralose-urethrane anesthesia. Both drug interventions reduced systemic blood pressure, heart rate, and left-ventricular dP/dt similarly. Occlusion of the left-anterior descending coronary artery alone did not change any of these hemodynamic variables. Although both drug interventions reduced ΣST, the reduction was statistically significantly greater with halothane than with nitroprusside-propranolol.

Key Words: ANESTHETIC TECHNIQUES: hypotensive, nitroprusside; ANESTHETICS, Volatile: halothane; SYMPATHETIC NERVOUS SYSTEM: sympatholytic agents, propranolol; ANESTHESIA; cardiovascular.

SURGERY during light anesthesia may result in sympathetic stimulation with concomitant increases in blood pressure, heart rate, myocardial contractility, and left-ventricular filling pressure. An increase in these indices of myocardial oxygen demand may prove particularly detrimental to patients with ischemic heart disease. Such unwanted responses may be controlled with deeper anesthesia or the administration of beta-adrenergic blocking agents and vasodilators. The administration of halothane, or an increase in its concentration, has been shown to reduce electrocardiographic signs of myocardial ischemia (1). Similarly, beta-blockers (2, 3) and vasodilators (4, 5) have reduced signs of myocardial ischemia in animal models and in man. There is little comparative information indicating which treatment is preferable.

We compared the effects of halothane with those of nitroprusside-propranolol on experimentally induced myocardial ischemia in dogs. Myocardial ischemia was induced by temporarily occluding the coronary artery using the model developed by Maroko et al (2). In this model, our index of ischemia was elevation of the epicardial ST segment.

Methods

We studied five large mongrel dogs (27 to 35 kg each). Anesthesia was induced with chloralose (90 mg/kg) and urethrane (900 mg/kg), the trachea was intubated, and ventilation was controlled (F_{IO_2} 1.0). Tidal volume was set at 500 to 600 ml, and respiratory frequency adjusted to provide a Pa_{CO_2} of 35 to 38 torr. Sodium bicarbonate was administered if base deficit exceeded −3.0 meq/L. Esophageal temperature was measured and maintained between 35.2 and 37.5 C using a heating blanket and lamp. The heart was exposed through a left thoracotomy in the fifth intercostal space. The pericardium was opened widely parallel to the phrenic nerve and the heart suspended in a cradle of pericardium. A portion of the left-anterior descending coronary artery (LADCA) was

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Supported in part by the Medical Research Service of the Veterans Administration.
Received from the Department of Anesthesia, State University of New York, Upstate Medical Center, Syracuse, New York; and Department of Anesthesia, University of California, San Francisco, California. Accepted for publication September 2, 1981.

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dissected free of its surrounding alveolar tissue, and a loose rubber-band tourniquet (3-mm wide) was placed around the artery. A small spring-loaded clamp placed on this rubber band occluded the LADCA. A sketch of the anterior surface of the heart was made showing both arterial and venous circulation. Eight to 10 sites were numbered at specific identifiable spots on the sketch (Fig 1) distal to the LADCA so that corresponding sites could be found on the myocardium. The junction of veins and arteries and the bifurcations provided reference points for the sites. Two of the sites were well outside the distribution of the LADCA. A transducer-tipped catheter was inserted into the left ventricle via the left atrium, and a #8 polypropylene catheter was placed in the thoracic aorta via the femoral artery.

Hemodynamic measurements included central aortic pressure, left-ventricular pressure (P_{LV}), the first derivative of P_{LV} (maximal positive dP/dt), and left-ventricular end-diastolic pressure (LVEDP). Maximal positive dP/dt was measured by differentiating the left-ventricular pressure signal with an active electronic differentiator; the positive deflection was calibrated (torr·sec^{-1}) using a triangular wave signal of known slope.

Following surgery, 45 to 60 minutes was allowed for stabilization of the preparation. Arterial blood gas tensions were again measured; ventilation was adjusted and bicarbonate administered according to the previously described criterion. Arterial blood gases were measured during each drug intervention to determine stability of oxygenation and ventilation. The esophageal temperature was kept constant throughout the remainder of the experiment. An epicardial electrocardiogram (ECG) was measured at each of the labeled sites using a hand-held saline wick that was calibrated at 1 mV = 1 mm and attached to a precordial lead (2). The LADCA was then occluded. After 3 and 6 minutes of occlusion, measurements were repeated at each site sequentially. Measurement of all the sites required 2 to 2.5 minutes. After 15 minutes, the occlusion of the LADCA was released and the sites were measured again. For each series of measurements, the sum of the measurements of the ST segments made before and after occlusion had to agree within 2 mV before the next part of the experiment was begun. ST segment measurements obtained at one site during occlusion and their return toward normal are shown in Fig 2.

Halothane anesthesia was administered until a stable end-tidal concentration of 1.1% was reached; this concentration was maintained for a minimum of 15 minutes. During this period, blood pressure, heart rate, LVEDP, and LV dP/dt remained constant. The LADCA was again occluded for 6 minutes at each site and ST segments were measured. Halothane was then discontinued, and after approximately 90 minutes (halothane < 0.08%), was considered gone.

Propranolol and sodium nitroprusside (N-P) were then administered so that values for heart rate and mean blood pressure were similar to those produced by halothane (1.1% end-tidal concentration). The mean dose of propranolol required to reduce the heart rate to the desired level was 0.34 mg/kg (range 0.13 to 1.1 mg/kg). The mean dose of nitroprusside ad-

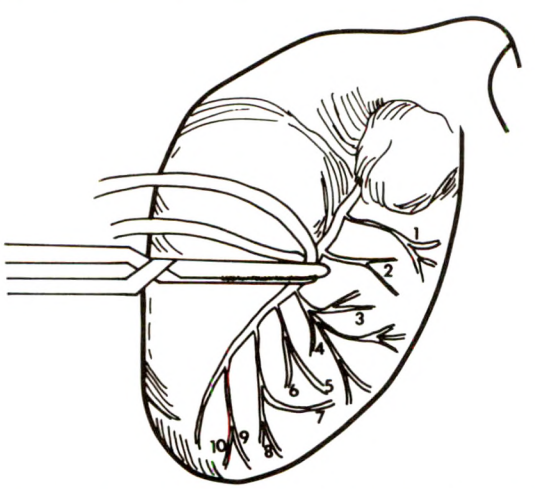


FIG 1. Diagrammatic sketch of anterior surface of left ventricle depicting left-anterior descending coronary artery, site of dissection, and labeling of measurement sites.

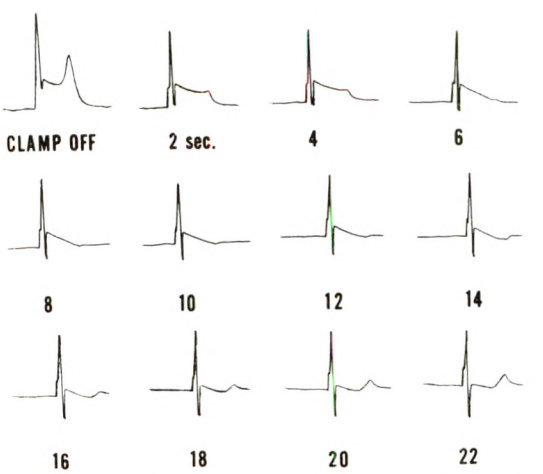


FIG 2. Marked elevation of ST segments occurs after 6 minutes of occlusion of left-anterior descending coronary artery (first ECG complex). Continuous measurements at this site were made during removal of clamp. ECG complexes are shown for each 2-second period. Return of ST segments to normal is rapid when circulation is re-established.

ministered to obtain the desired blood pressure was 38.9 μg/kg/min (range 6.9 to 59.2 μg/kg/min). The LADCA was again occluded and epicardial ECG measured after 3 and 6 minutes of occlusion. Statistical analysis was performed with factorial analysis of variance (6).

Results

Arterial P_{O_2} was always greater than 250 torr, and after completion of surgery, Pa_{CO_2}, pH, and esophageal temperature were kept constant throughout the experiment. Occlusion of the coronary artery always produced a cyanotic area of paradoxically moving left ventricle distal to the occlusion site. Values for hemodynamic variable and ΣST segments are shown in the Table. Systemic blood pressure, heart rate, LV dP/dt, and LVEDP were not changed by occlusion of the LADCA. Hemodynamic values were similar for halothane and N-P. Although ΣST was reduced by both halothane and N-P, the reduction was statistically significantly greater with halothane (Table and Fig 3). In all animals, the increase in ΣST with occlusion was less with halothane than with N-P.

Discussion

We compared the effects of two drug interventions on electrocardiographic criteria of myocardial ischemia. Both interventions reduced systolic blood pressure, heart rate, and LV dP/dt similarly, as intended. Both interventions also reduced coronary artery perfusion pressure (systemic diastolic pressure − LVEDP) similarly. Although ΣST was reduced by both interventions, the reduction was statistically significantly greater with halothane, despite the fact that both interventions produced similar values for the indices of myocardial oxygen supply and demand. We postulate three possible explanations.

The first explanation might be that halothane has a beneficial effect that is separate from its effect on indices of myocardial oxygen supply and demand. Recent work by Verrier et al (7) demonstrated that halothane anesthesia provided a greater coronary vascular reserve than did a barbiturate-nitrous oxide-relaxant technique. These investigators measured coronary vascular conductance (coronary blood flow/coronary diastolic pressure) during maximal coronary vasodilation. At similar levels of pressure, the flow was always greater with halothane. Heart rate was reduced in animals anesthetized with halothane, and this reduction was thought to be a major factor in the greater vascular reserve achieved with halothane. However, in our study, heart rate was identically affected by both regimens. Whether a favorable effect of halothane on coronary vascular conductance is the mechanism by which electrocardiographic evidence of myocardial ischemia is reduced is unknown.

A second possible explanation is that halothane may have a nonspecific effect on ST segments that is not related to relief of ischemia. There is an impressive body of literature, however, relating changes in ST segments to other measures of ischemia. Wegria et al (8) reported an inverse correlation between elevation of ST segments and coronary blood flow when the latter was controlled by external perfusion. Timogiannakis and co-workers (9) examined regional blood flow during partial coronary occlusion and found an inverse correlation between regional flow and elevation of ST segments. Although other investigators have also described inverse correlations between elevation of ST segments and coronary blood flow (10, 11), the correlations were not strong (12). Elevations of ST segments have also been noted to correspond with lactate production (13) and myocardial tissue P_{O_2} (14, 15). In describing the use of ΣST

TABLE

Effect of 6 Minutes of Coronary Artery Occlusion*

Anesthetic	Reduction in ST increase from chloralose-urethrane	Maximal positive left-ventricular dP/dt	Systolic pressure	Diastolic pressure	Heart rate	Left-ventricular end-diastolic pressure
	mV	*torr/sec*	*torr*		*beats/min*	*torr*
Chloralose-urethrane	—	2852	131.0	102.0	192.0	9.5
	—	±202	±4.2	±3.0	±4.9	±2.7
1.1% halothane	31.6†‡	1061†	81.4†	58.0	136.0†	8.5
	±5.8	±1	±3.7	±3.1	±5.8	±3.6
Nitroprusside-propranolol	18.3†	1376†	80.4†	53.8	136.0†	7.0
	±5.4	±72	±3.2	±3.4	±4.0	±1.8

* Values are means ± SE. Statistical significance was determined using analysis of variance.

† Significantly different from values obtained during chloralose-urethrane anesthesia ($p < 0.05$).

‡ Significantly greater than value for nitroprusside-propranolol ($p < 0.05$).

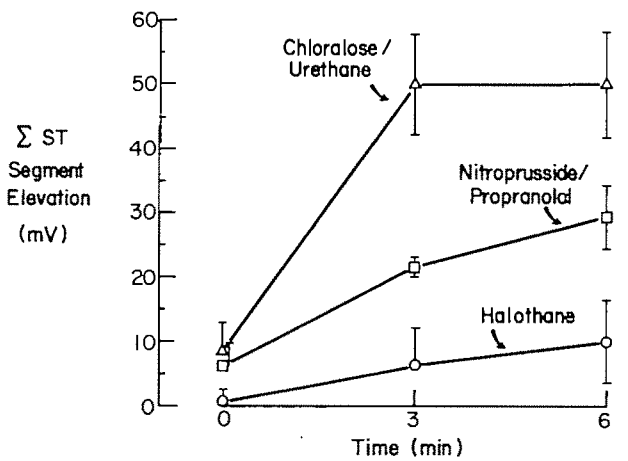


FIG 3. ΣST in response to coronary artery occlusion. Nitroprusside-propranolol and halothane significantly limit increase in ΣST at both 3 and 6 minutes when compared with measurements made during chloralose-urethrane anesthesia ($p < 0.05$). Reduction in ΣST is statistically significantly greater with halothane than with nitroprusside-propranolol at 6 minutes ($p < 0.05$).

segments to measure myocardial ischemia, Maroko et al (2) determined a correlation between elevation of ST segments and histologic and biochemical evidence of ischemia. However, there are no studies that compare elevation of ST segments with other biochemical or histologic markers as an index of ischemia during the administration of halothane.

Third, through direct vasodilation of the coronary artery, sodium nitroprusside may have contributed to faulty distribution of myocardial blood flow. Using the xenon-133 washout technique, Mann et al (16) studied regional myocardial blood flow in patients and concluded that nitroprusside could result in redistribution of blood flow away from ischemic areas. Chiariello and co-workers (17) examined the effect of nitroprusside on ischemic injury in myocardial infarction produced by coronary artery occlusion in open-chested dogs. Nitroprusside was found to increase elevation of the ST segment and to reduce endocardial blood flow in the ischemic region of the myocardium. Therefore, some degree of faulty regional distribution is probably responsible for the less favorable effect seen in those dogs receiving nitroprusside.

In this study, we always administered halothane before we administered nitroprusside-propranolol. Although it would be desirable to reverse this order, the duration of action of propranolol would make this impractical. We believe this approach was justified, as other investigators (2, 18) and ourselves (Gerson JI, Hickey RF, Bainton CR: The effect of halothane on heart ischemia and oxygen supply/demand ratio. Abstracts of Scientific Papers, Annual Meeting of the American Society of Anesthesiologists, October 21-25, 1978, Chicago, Illinois, pp 283-4) have demonstrated the stability of the preparation to repeated occlusions. We restricted our coronary artery occlusion time to 6 minutes because maximum ΣST appeared to be achieved by this time, and shorter periods of occlusion would produce less damage to the myocardium. Deterioration of the preparation was not indicated by changes in the ST segment in the control state (i.e., before occlusion). Finally, as ischemia progresses to infarction, ST segments return toward base line. Thus, deterioration of the preparation would produce less elevation of ST segments in response to occlusion. The last drug intervention we studied (nitroprusside-propranolol) produced a greater increase in ΣST segments than did halothane. Preparation deterioration with time would have produced results directly opposite to these, and so cannot be responsible for our finding.

Transfer of findings from this work to the clinical setting should be done cautiously with realization of study limitations. An animal model of acutely induced myocardial ischemia is very different from the myocardial ischemia seen in coronary artery disease in man. Nevertheless, this study indicates that halothane may possess some favorable properties that permit control of unwanted circulatory responses to surgical stimuli adversely affecting the ischemic heart with good ventricular function.

In conclusion, we found that elevation of ST segments was more limited with halothane than with a combination of nitroprusside and propranolol. We achieved, by study design, similar indices of myocardial oxygen demand and supply using halothane or nitroprusside-propranolol. We believe the more favorable effect of halothane can be explained by its effects on coronary vascular reserve (5) and the known effect of nitroprusside to reduce myocardial blood flow to ischemic myocardium (14, 15).

REFERENCES

1. Kistner JR, Miller ED, Lake CL, Ross WT Jr. Indices of myocardial oxygenation during coronary-artery revascularization in man with morphine versus halothane anesthesia. Anesthesiology 1979;50:324-30.
2. Maroko PR, Kjekshus JK, Sobel BE, et al. Factors influencing infarct size following experimental coronary artery occlusions. Circulation 1971;43:67-82.
3. Reimer KA, Rasmussen MM, Jennings RB. Reduction by propranolol of myocardial necrosis following temporary coronary artery occlusion in dogs. Circ Res 1973;33:353-63.
4. Becker LC. Effect of nitroglycerine and dipyridamole on regional left ventricular blood flow during coronary artery occlusion. J Clin Invest 1976;58:1287-96.

5. Awan NA, Miller RR, Zakauddin V, DeMaria AN, Amsterdam EA, Mason DT. Reduction of S-T segment elevation with infusion of nitroprusside in patients with acute myocardial infarction. Am J Cardiol 1976;38:435-9.
6. Snedecor GW, Cochran WG. Statistical methods. Ames, IA: Iowa State University Press, 1967.
7. Verrier ED, Edelist G, Consigny PM, Robinson S, Hoffman JIE. Greater coronary vascular reserve in dogs anesthetized with halothane. Anesthesiology 1980;53:445-59.
8. Wegria R, Segers M, Keating RP, Ward HP. Relationship between the reduction in coronary flow and the appearance of electrocardiographic changes. Am Heart J 1949;38:90-6.
9. Timogiannakis G, Amende I, Martinez E, Thomas M. ST segment deviation and regional myocardial blood flow during experimental partial coronary occlusion. Cardiovasc Res 1974;8:469-77.
10. Kjekshus JK, Maroko PR, Sobel BE. Distribution of myocardial injury and its relation to epicardial ST-segment changes after coronary artery occlusion in the dog. Cardiovasc Res 1972;6: 490-9.
11. Becker LC, Ferreira R, Thomas M. Mapping of left ventricular blood flow with radioactive microspheres in experimental coronary artery occlusion. Cardiovasc Res 1973;7:391-400.
12. Smith HJ, Singh BN, Norris RM, John MB, Hurley PJ. Changes in myocardial blood flow and S-T segment elevation following coronary artery occlusion in dogs. Circ Res 1975;36:697-705.
13. Scheuer J, Brachfeld N. Coronary insufficiency: relations between hemodynamic, electrical, and biochemical parameters. Circ Res 1966;18:178-89.
14. Sayen JJ, Pierce G, Katcher AH, Sheldon WF. Correlation of intramyocardial electrocardiograms with polarographic oxygen and contractility in the nonischemic and regionally ischemic left ventricle. Circ Res 1961;9:1268-79.
15. Angell CS, Lakatta EG, Weisfeldt ML, Shock NW. Relationship of intramyocardial oxygen tension and epicardial ST segment changes following acute coronary artery ligation: effects of coronary perfusion pressure. Cardiovasc Res 1975;9:12-8.
16. Mann T, Cohn PF, Holman BL, Green LH, Markis JE, Phillips DA. Effect of nitroprusside on regional myocardial blood flow in coronary artery disease.Circulation 1978;57:732-8.
17. Chiariello M, Gold HK, Leinbach RC, DAvis MA, Maroko PR. Comparison between the effects of nitroprusside and nitroglycerin on ischemic injury during acute myocardial infarction. Circulation 76;54:766-73.
18. Ergin MA, Dastgir G, Butt KMH, Stuckey JH. Prolonged epicardial mapping of myocardial infarction: the effects of propranolol and intra-aortic balloon pumping following coronary artery occlusion. J Thorac Cardiovasc Surg 1976;72:892-9.

Labor Pain and Prepared Childbirth Training

Labor pain was assessed with the McGill Pain Questionnaire in 87 primiparas and 54 multiparas. Patients were studied in the obstetric unit of a large teaching hospital. The average intensity of labor pain ranked among the most intense pains recorded with the questionnaire. However, the pain scores had a wide range and were influenced by several medical and social variables. They were significantly higher for the primiparas than for the multiparas. Moreover, high pain levels were associated with a history of menstrual difficulties and lower socioeconomic status. The primiparas who had received prepared childbirth training had lower pain scores than those who had received no such training. Nevertheless, the effects of prepared childbirth training were relatively small, and most patients (81%) who received it requested epidural anesthesia. Because many women who received training suffered severe pain during labor, prepared childbirth training and epidural anesthesia should be regarded as compatible, complementary procedures. *(Melzack R, Taenzer P, Feldman P, Kinch RA: Labour is still painful after prepared childbirth. Can Med Assoc J 1981;125:357-63)*

ANESTH ANALG
1982;61:15–8

A Controlled Comparison of the Effects of Extradural Diamorphine and Bupivacaine on Plasma Glucose and Plasma Cortisol in Postoperative Patients

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COWEN, M. J., BULLINGHAM, R.E.S., PATERSON, G.M.C., MCQUAY, H. J., TURNER, M., ALLEN, M. C., AND MOORE, A.: A controlled comparison of the effects of extradural diamorphine and bupivacaine on plasma glucose and plasma cortisol in postoperative patients. Anesth Analg 1982;61:15–8.

The effects of an extradural narcotic, diamorphine, and of an extradural local anesthetic, bupivacaine, on postoperative responses of plasma glucose and cortisol levels following surgery were investigated in 20 fit women undergoing major gynecologic operations. The operations were conducted with morphine premedication and extradural local anesthetic with nitrous oxide, oxygen, and halothane. After surgery the patients were given either further extradural local anesthetic or 5 mg of extradural diamorphine. After surgery plasma glucose and plasma cortisol concentrations decreased in patients given extradural diamorphine, but increased in those given extradural local anesthetic. The differences between the groups were statistically highly significant ($p < 0.05$) for both glucose and cortisol. The effects on metabolic responses to surgery produced by a small (5 mg) dose of diamorphine injected into the extradural space suggest a local action of the narcotic at the level of the spinal cord. Only very large intravenous doses of narcotics have previously been shown to suppress these responses.

Key Words: ANESTHETIC TECHNIQUES: epidural; ANALGESICS: narcotic: heroin; METABOLISM: glucose, cortisol.

CLINICAL use of extradural and intrathecal opiates followed the discovery of opiate receptors in the spinal cord (1). A major problem in interpreting the analgesic efficacy of extradural narcotics is that systemic concentrations of the narcotics following extradural administration resemble those following intramuscular administration (2–4). This must contribute some proportion of the total analgesic effect, but the exact extent is a matter of conjecture.

Diamorphine (diacetylmorphine, heroin) is rapidly metabolized after parenteral administration to monoacetyl morphine and morphine (5), and has a potency and duration of action similar to that of morphine. Diamorphine is, however, considerably more lipophilic than morphine, and high lipophilicity would seem an advantageous property for dural penetration for narcotics used extradurally. Diamorphine has been shown to have long-lasting effects when given extradurally to patients with chronic pain (6).

This study reports a controlled clinical evaluation of the effects of extradural diamorphine given after surgery on the postoperative responses of plasma glucose and plasma cortisol levels in comparison with the local anesthetic, bupivacaine. It demonstrates that the responses following extradural diamorphine differ significantly from those known to occur with parenteral use.

Patients and Methods

Twenty fit patients undergoing major abdominal gynecologic surgery (16 total abdominal hysterecto-

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Supported by the Medical Research Council (H.J.M.) and (M.C.A.) and supported in part by a Regional Health Authority locally organized research grant.

Received from the Nuffield Departments of Anaesthetics and Clinical Biochemistry, Radcliffe Infirmary, Oxford, United Kingdom. Accepted for publication September 7, 1981.

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mies, four others) at the Churchill Hospital, Oxford, were studied; informed consent was obtained from each patient and the study was approved by the local Ethics Committee. The patients were assigned alternatively into one of two groups. After surgery, patients in group 1 received extradural diamorphine and those in group 2 received extradural bupivacaine. Patients were excluded if they suffered severe cardiovascular, respiratory, hepatic, or renal disease, or diabetes, or if they were receiving corticosteroid treatment.

Premedication consisted of morphine, 10 mg, and hyoscine, 0.2 mg, by single intramuscular injection 1 hour before surgery. Intraoperative anesthesia consisted of extradural blockade combined with a light general anesthetic. With the patient in the lateral position an extradural catheter with filter was inserted at the level of the L2-3 space. A test dose of 2 ml of a 1:1 v/v mixture of 1.5% plain lignocaine and 0.5% plain bupivacaine was given after the patient was turned into the supine position; this was followed in 3 minutes by 15 to 20 ml of the same mixture. Sample times were determined from this moment. Sensory levels of approximately T-8 resulted. Induction of general anesthesia, 10 minutes after the major injection of local anesthetic, was with 5 mg/kg of intravenous thiopentone. Maintenance was with nitrous oxide and oxygen (2:1) at 100 ml/kg administered via a Bain coaxial breathing circuit using a facemask and oropharyngeal airway. Halothane was added as required.

After surgery, i.e., 3 hours after the extradural injection of 15 to 20 ml of local anesthetic solution, patients in group 1 were given a further extradural injection via the catheter of 5 mg of diamorphine in 10 ml of sterile water and patients in group 2 were given 10 ml of 0.25% plain bupivacaine.

Blood samples were taken from an indwelling intravenous cannula (*a*) before induction of general anesthesia; (*b*) 30, 60, 120, and 180 minutes after the extradural injection of 15 to 20 ml of local anesthetic solution; and (*c*) 60, 120, 180, and 240 minutes after the extradural injection of either diamorphine or bupivacaine. Samples were collected into lithium heparin and fluoride oxalate tubes and stored in the cold until separated.

Plasma cortisol levels were measured by a competitive protein binding technique (7) and plasma glucose levels were measured using a Beckman glucose analyser. Plasma morphine equivalents of diamorphine and its metabolites were measured by radioimmunoassay using antiserum obtained from Guildhay Antisera (Guildford, Surrey); this antiserum cross-reacted equally with morphine, diamorphine, monoacetylmorphine, and codeine, and also, to a much smaller extent, with morphine glucuronide. Morphine sulfate was used as the standard.

Statistical analysis was with Student's *t*-test.

Results

There was no significant difference between the groups for age, weight, or other demographic variables (Table 1).

There were no statistically significant differences between the two groups of patients for cortisol or glucose in the first 3 hours. There was an overall increase of some 300 to 400 nmol/L in plasma cortisol and 1.1 mmol/L in plasma glucose in each group (Table 2).

However, after the postoperative extradural dose of either diamorphine or bupivacaine large differences became apparent. After diamorphine the cortisol and glucose levels decreased, whereas after bupivacaine both measurements showed large increases in the 4 hours after surgery. The differences between the groups were statistically significant after the second extradural injection [$p < 0.05$ for cortisol at 60, 120, and 180 minutes (Fig 1) and for glucose at 120, 180, and 240 minutes (Fig 2)].

Plasma morphine equivalents measured as morphine base were of the order of 100 ng/ml or less for all samples taken in patients in group 1 after extradural diamorphine.

Discussion

The changes found here for plasma glucose and cortisol levels in patients treated with extradural bupivacaine alone are in accord with results published by others who likewise studied patients undergoing abdominal hysterectomy with a similar dose of extradural local anesthetic (8); the changes are typical of those seen in moderate-to-severe surgical procedures.

TABLE 1
Patient Data.*

	Group 1	Group 2
No. of patients	10	10
Age (yr)	43.0 ± 1.7	43.4 ± 3.8
Weight (kg)	64.6 ± 2.8	64.9 ± 3.9
Height (cm)	162.5 ± 2.4	161.3 ± 2.6
Surgery time (min)	81 ± 5	72 ± 6
Blood loss (ml)	230 ± 93	208 ± 46

* Values are means ± SEM.

TABLE 2
Plasma Cortisol and Glucose Levels*

Time	Cortisol			Glucose		
	Group 1	Group 2	p	Group 1	Group 2	p
min	*nmol/L*			*mmol/L*		
1st extradural						
0	345 ± 31	378 ± 51	NS	4.82 ± 0.28	4.77 ± 0.22	NS
30	247 ± 39	242 ± 32	NS	5.04 ± 0.28	5.11 ± 0.26	NS
60	270 ± 62	398 ± 73	NS	5.30 ± 0.33	5.28 ± 0.26	NS
120	550 ± 81	713 ± 64	NS	5.95 ± 0.51	5.78 ± 0.25	NS
180	635 ± 111	794 ± 73	NS	5.97 ± 0.54	5.89 ± 0.54	NS
2nd extradural						
60	516 ± 81	870 ± 67	<0.01	5.21 ± 0.36	5.90 ± 0.23	<0.2
120	442 ± 77	1187 ± 178	<0.01	5.01 ± 0.27	6.52 ± 0.41	<0.05
180	553 ± 100	1118 ± 144	<0.01	5.15 ± 0.23	6.77 ± 0.35	<0.001
240	717 ± 104	1050 ± 144	<0.1	5.41 ± 0.28	6.86 ± 0.35	<0.01

* Results are means ± SEM, with 10 patients in each group. Significance was calculated using a two-tailed Student's *t*-test. (Conversion factors: cortisol, 1 nmol/L = 0.036 μg/100 ml; glucose, 1 mmol/L = 18.0 mg/100 ml). First extradural for both groups was 15 to 20 ml of plain bupivacaine. Second extradural was 10 ml of water containing 5 mg of diamorphine for group 1, and 10 ml of plain bupivacaine for group 2.

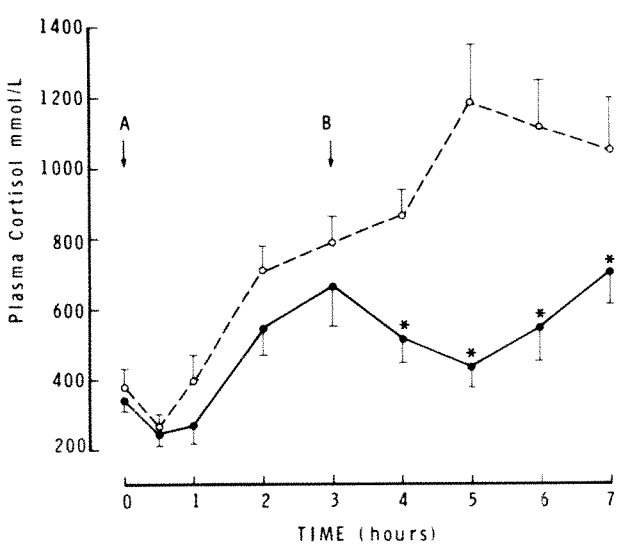


FIG 1. Plasma cortisol concentrations in group 1 (– – –) and group 2 (——) patients during and after operation. Arrows show first (A) and second (B) extradural injections. * Statistical significance, $p < 0.05$, between groups.

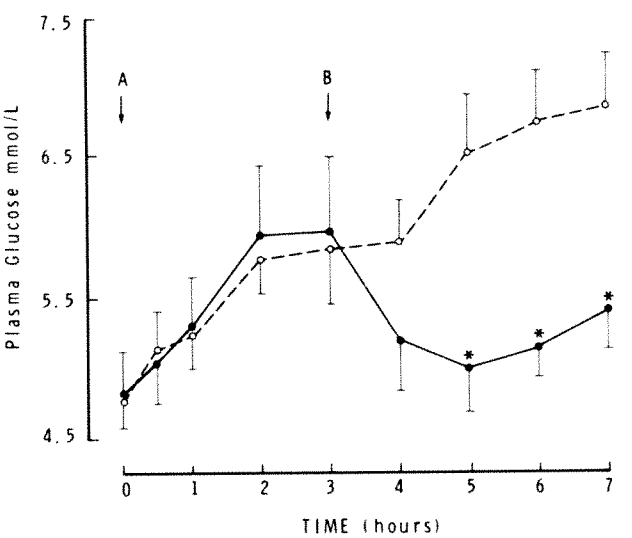


FIG 2. Plasma glucose concentrations in group 1 (– – –) and group 2 (——) patients during and after operation. Arrows show first (A) and second (B) extradural injections. * Statistical significance, $p < 0.05$, between groups.

Similar groups of patients undergoing a general anesthetic without spinal local anesthetic, but with fentanyl analgesia, had similar changes in plasma cortisol (9). Extradural injections of large volumes (40 ml) of local anesthetics that produce nerve blocks extending from the cervical to sacral levels must be used in order to suppress the glycoregulatory response to surgery using this technique. This is a much larger volume than that used here. In addition, halothane anesthesia is known not to influence metabolic changes (10).

The injection of a small (5 mg) dose of diamorphine in 10 ml of distilled water gave a significant suppression of the glycoregulatory stress response. There are no previous reports of extradural opiate use resulting in suppression of the endocrine and metabolic response to surgery.

Large doses of opiate agonists given intravenously can cause suppression of the glycoregulatory response to surgical stress (10–12). The doses of intravenous opiate required to achieve this effect are, typically, 4 mg/kg for morphine and more than 50 μg/kg for fentanyl. These are some 20 to 50 times greater than usual parenteral doses and may be expected to give

high plasma opiate concentrations. The amount of narcotic administered for extradural use is small by comparison; in this study the mean diamorphine dose was less than 0.1 mg/kg. The 5-mg dose given is a normal parenteral dose for diamorphine.

However, in exceptional circumstances high plasma levels can result from extradural narcotic administration (4). Such events may produce brain opiate concentrations similar to those after large intravenous doses. It was therefore necessary to demonstrate that the effects obtained here on the glycoregulatory response to surgery were not an artifact. No patient receiving extradural diamorphine in this trial had plasma levels of morphine equivalents that could account for the observed suppression. The antiserum used cross-reacted to the known metabolites of diamorphine (principally monoacetylmorphine and morphine), but the observed levels were similar to those obtained for extradural morphine measured by a chromatographic technique (2).

Hence the large and statistically significant effects of a small dose (5 mg) of extradural diamorphine on two of the major indices of the glycoregulatory endocrine response to surgery must be due to a local action at the level of the spinal cord. This is corroboration for the spinal action of opiates independent of measurements of analgesia or side effects such as itching, vomiting, or urinary retention, all of which are notoriously difficult to quantify.

The mechanism for the analgesic action of extradural narcotics involves a specific opiate receptor (13). The suppressive effects of large parenteral doses of narcotic agonists may be mediated through this same spinal receptor; high plasma levels may result in appreciable drug levels in the spinal cord.

Diamorphine is progressively deacetylated to monoacetylmorphine (MAM) and then to morphine (14). These enzymatic hydrolyses occur in many tissues including those of the neuraxis. The conversion of diacetylmorphine to MAM is extremely rapid, so rapid that brain levels of diamorphine are barely detectable after a parenteral dose in rats (14), or in urine after intravenous infusion in man (15). On the other hand, appreciable levels of MAM occur in rat brain after parenteral injection of diamorphine: peak levels were reported to occur within 15 minutes, and then decayed with a half-life of approximately 70 minutes. In man the levels of MAM seen in urine after intravenous infusion achieve a cumulative total of a few percent only of the administered diamorphine dose (15). The pharmacologic effects of systemic diamorphine administration correlate with brain morphine concentrations rather than with diamorphine or MAM concentrations. Although a specific action of MAM in producing the effects noted here cannot be excluded: (*a*) MAM is still a narcotic, and the argument for a local action at cord level would still apply. (*b*) It is unlikely that these effects are MAM mediated in view of the lability of MAM compared with the persistence of the described effects.

In conclusion, this work does suggest another useful dimension for the investigation of the actions of spinal narcotics.

ACKNOWLEDGMENTS

We wish to thank Professor A. C. Turnbull for allowing us to study his patients, and the patients for helping us. We thank the nursing staff of Ward 15 and the recovery room for their help.

REFERENCES

1. Yaksh TL, Rudy TA. Analgesia mediated by a direct spinal action of narcotics. Science 1976;192:1357–8.
2. Weddel SJ, Ritter RR. Serum levels following epidural administration of morphine and correlation with postsurgical pain relief. Anesthesiology 1981;54:210–4.
3. Cousins MJ, Mather LE, Glynn CJ, Wilson PR, Graham JR. Selective spinal analgesia. Lancet 1979;1:1141–2.
4. Bullingham RES, McQuay HJ, Moore RA. Unexpectedly high plasma fentanyl levels after epidural use. Lancet 1980;1:1361–2.
5. Boerner U, Abbott S, Roe RL. The metabolism of morphine and heroin in man. Drug Metab Rev 1975;4:39–73.
6. McQuay HJ, Bullingham RES, Evans PJD, Lloyd JW, Moore RA. Demand analgesia to assess pain relief from epidural opiates. Lancet 1980;1:768–9.
7. Beardwell CG, Burke CW, Cope CL. Urinary free cortisol measured by competitive protein binding. J Endocrinol 1968;42:79–89.
8. Brandt MR, Kehlet H, Binder C, Hagen C, McNeilly AS. Effect of epidural analgesia on the glycoregulatory endocrine response to surgery. Clin Endocrinol 1976;5:107–14.
9. McQuay, HJ, Moore RA, Paterson GMC, Adams AP. Plasma fentanyl levels and clinical observations during and after surgery. Br J Anaesth 1979;51:543–50.
10. Hall GM, Young C, Holdcroft A, Alaghband-Zadeh J. Substrate mobilisation during surgery. Anaesthesia 1978;33:924–30.
11. George JM, Reier CE, Larese RR, Rower JM. Morphine anaesthesia blocks cortisol and growth hormone responses to surgical stress in humans. J Clin Endocrinol Metab 1974;38:736–41.
12. Stanley TH, Berman L, Green O, Robertson D. Plasma catecholamine and cortisol responses to fentanyl-oxygen anesthesia for coronary artery operation. Anesthesiology 1980;53:250–3.
13. Yaksh TL, Jessell TM, Gamese R, Mudge AW, Leeman S. Intrathecal morphine inhibits substance P release from mammalian spinal cord in vivo. Nature 1980;286:155–6.
14. Way, EL, Young JM, Kemp JW. Metabolism of heroin and its pharmacologic implications. Bull Narcotics 1965;17:25–33.
15. Elliot HW, Parker KD, Wright JA, Nomof N. Actions and metabolism of heroin administered by continuous intravenous infusion to man. Clin Pharmacol Ther 1971;12:806–14.

ANESTH ANALG
1982;61:19-22

Lack of Toxicity of Enflurane on Male Reproductive Organs in Mice

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BADEN, J. M., LAND, P. C., EGBERT, B., KELLEY, M., AND MAZZE, R. I.: Lack of toxicity of enflurance on male reproductive organs in mice. Anesth Analg 1982;61:19-22.

Enflurane has been shown to increase slightly the percentage of abnormal spermatozoa in mice. To examine in more detail possible adverse effects of enflurane on male reproductive organs, 125 Swiss/ICR mice were exposed to 0.3% enflurane for up to 18 months; a control group of 125 mice was exposed concurrently to air. Exposures were for 4 hours/day, 5 days/week. After 12 months of exposure, groups of 25 enflurane-treated and control mice were killed, and chromosomal analysis of spermatogonial cells was performed. After 18 months exposure, remaining mice were killed and epididymal sperm were collected for morphologic examination. In addition, the reproductive organs of all mice dying or killed throughout the study were examined histologically. Approximately 1% of spermatogonial cells from both enflurane-treated and control mice had aberrant chromosomes. The average percentage of morphologically abnormal sperm was 9.4 ± 1.7 for enflurane-treated mice and 6.5 ± 1.3 for control mice; the difference was not statistically significant ($p = 0.18$). Finally, there was no difference between the treated and control mice in histologic appearance of reproductive organs. It was concluded that long-term exposure to enflurane has no adverse effects on male reproductive organs in mice.

Key Words: ANESTHETICS, Volatile: enflurane; TOXICITY: enflurane.

RESULTS of epidemiologic surveys of operating room and dental personnel have led to the suggestion that adverse reproductive effects occur in the male exposed to waste anesthetic gases (1-3). The evidence is based on the findings that there may be a higher incidence of spontaneous abortions in wives of exposed individuals and that congenital abnormalities may be more frequent in their offspring. In addition, it has been demonstrated that long-term exposure of rats to nitrous oxide affects spermatogenesis (4) and that exposure to a combination of nitrous oxide and halothane causes chromosome aberrations in spermatogonia (5). Even enflurane, which is generally regarded as a volatile anesthetic of low toxicity, has been shown to increase slightly the percentage of abnormal spermatozoa in mice (6). In the present study, we have used an animal model to examine further the effects of enflurane on male reproductive tissue.

Methods

Two hundred fifty weanling male Swiss/ICR mice (Hilltop Labs, Chatsworth, CA) were divided randomly into two groups each containing 125 animals. Throughout the experiment, mice were housed four to a cage and were bedded on ground corn cob in polypropylene plastic cages with zinc-coated lids. They were fed small animal chow and allowed to drink tap water ad libitum, except during exposure when food and water were removed. The animals were on a fixed diurnal cycle of 12 hours light and 12 hours darkness with exposures during the light phase.

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Received from the Departments of Anesthesia, Stanford University School of Medicine, Stanford, California, and Northwestern University Medical School, Chicago, Illinois, and Anesthesiology and Pathology Services, Veterans Administration Medical Center, Palo Alto, California. Accepted for publication September 9, 1981.

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Group 1 (control) was exposed to medical grade compressed air and group 2 was exposed to 0.3% (3000 ppm) enflurane vapor in air. Enflurane was the commercially available product obtained from Ohio Medical Products, Madison, WI. Exposure was for 4 hours/day, 5 days/week. This study was performed in conjunction with a lifetime carcinogenicity assay and the exposure regimen was determined in preliminary studies as one that provided the maximum tolerated dose of enflurane.

Exposures were performed in two 1500-L capacity, airtight stainless steel and Plexiglas chambers. One chamber was used exclusively for the enflurane exposures. At each exposure, cages were placed randomly in the chambers. Enflurane was vaporized with medical grade compressed air using a Copper Kettle vaporizer and was conducted to the chamber through rubber tubing. An electric fan at each end of the chamber ensured uniform distribution of enflurane vapor. Enflurane concentration was determined using a Varian 1440 gas chromatograph and was checked every few minutes until it reached the desired concentration. This usually occurred by the 10th minute. Throughout exposure, enflurane concentration was maintained within a 5% tolerance limit, and temperature and humidity were maintained at 25 ± 2 C and 50% ± 10%, respectively. Carbon dioxide concentration was always less than 0.3%. At the end of exposure, the enflurane chamber was exhausted to a fume hood for 15 minutes before the door was opened and the animals were removed.

After 52 weeks of gassing, an interim sacrifice was performed. Ten animals in each group were administered colchicine, 2 mg/kg, intraperitoneally in distilled water and 5 hours later, these along with 15 additional animals from each group were weighed, then killed by asphyxiation with carbon dioxide. Their testes, epididymides, and seminal vesicles were removed and weighed. One testis from each colchicine-pretreated mouse was processed for spermatogonial chromosome analysis and all other reproductive organs were fixed in 10% buffered formalin. After 78 weeks of gassing, all remaining animals were weighed and killed. Fourteen mice from the control group and 12 from the enflurane group were selected randomly and their right cauda epididymis was placed in normal saline for analysis of sperm morphology. The remaining reproductive organs from these and all reproductive organs from the other animals killed, were weighed and fixed in 10% buffered formalin. Complete histologic examination was performed on the reproductive organs of animals killed and also on the reproductive organs of animals dying unexpectedly throughout the study.

Chromosome slides were prepared by the technique described by Coate et al (5). At least 50 spermatogonial cells in metaphase were assessed from each animal. Chromatid and chromosome breaks and other morphologic abnormalities of chromosomes were noted. Duplicate slides of cauda epididymal sperm were prepared from each animal by the method of Land et al (6). One thousand sperm on each slide were evaluated for abnormal morphology. Histologic sections of reproductive organs were prepared by standard methods and examined by a pathologist experienced in animal pathology.

Animal autopsies and examination of chromosome, sperm, and histology slides were performed by investigators who were not aware of the treatment group from which animals or specimens came. Student's t-test was used for intergroup comparisons; $p < 0.05$ was considered statistically significant.

Results

Mean body weight of enflurane-treated mice was slightly but significantly ($p < 0.01$) less than that for control mice both after 52 and 78 weeks of exposure (Table). Mean wet weights of seminal vesicles, testes, and epididymides were not significantly different

TABLE
Weights (g) of Study Mice*

Exposure	Body	Seminal vesicles	Epididymis	Testis
52 weeks				
Control (n = 25)	48.2 ± 0.8	0.48 ± 0.03	0.12 ± 0.01	0.15 ± 0.01
Enflurane (n = 25)	44.5 ± 0.6†	0.43 ± 0.03	0.11 ± 0.02	0.14 ± 0.01
78 weeks				
Control (n = 74)	47.5 ± 0.7	0.45 ± 0.04	0.11 ± 0.01	0.13 ± 0.01
Enflurane (n = 77)	42.0 ± 0.5†	0.41 ± 0.02	0.11 ± 0.01	0.13 ± 0.01

* Values are means ± SEM.
† Significantly less than control, $p < 0.01$.

(Table). On gross examination, all mice appeared to have normal reproductive organs with the exception of two control and three enflurane-treated mice with bilaterally small testes. On histologic examination, bilateral testicular atrophy with severe damage to the seminiferous tubules was observed. Compared with normal tubules (Fig 1), the affected tubules (Fig 2) were smaller and contained fewer spermatogonia and spermatids. Their lumina were wider and contained almost no mature sperm. Histologic examination of the remaining mouse testes revealed additional abnormalities in three control mice and one enflurane-treated mouse. The abnormalities included a sperm granuloma and focal deposition of calcium. None of the abnormalities appeared to be related to enflurane exposure. Other reproductive tissues examined after 52 and 78 weeks exposure were normal.

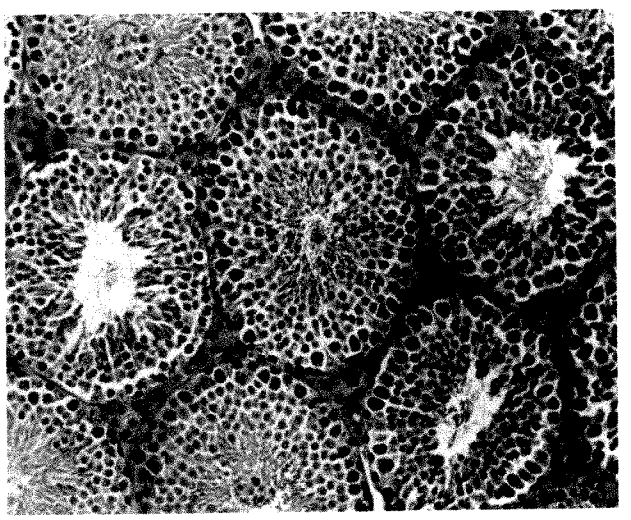


FIG 1. Normal testis from mouse exposed to enflurane for 18 months. All seminiferous tubules are lined with normal cells and lumina of many seminiferous tubules contain mature sperm (hematoxylin and eosin; 160×).

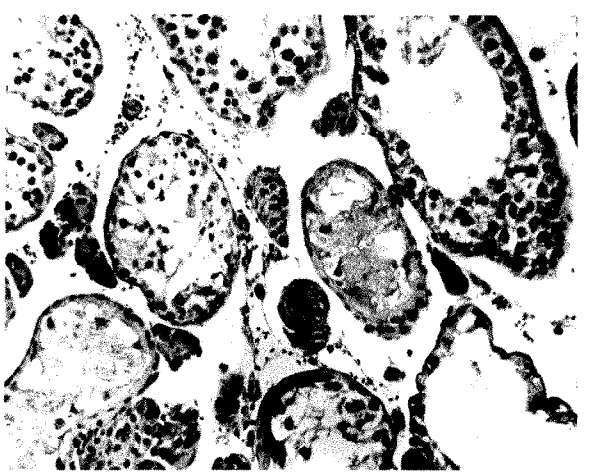


FIG 2. Testis from mouse with bilateral testicular atrophy. Seminiferous tubules contain reduced numbers of spermatogonia and spermatids, and no mature sperm (hematoxylin and eosin; 160×).

Three of 10 control mice and two of 10 enflurane-treated mice had one or more spermatogonial cells with aberrant chromosomes. There were a total of six aberrant cells among the 500 counted for the control group and five aberrant cells of the 500 counted for the treated group. The numbers of specific abnormalities were too small to allow a meaningful statistical analysis. There was clearly, though, no enflurane-related effect.

The percentage of morphologically abnormal sperm from each animal is shown in Fig 3. The mean abnormality rate for enflurane-exposed mice was 9.4 ± 1.7 (SE) (n = 12). This rate was slightly higher than for control mice, 6.5 ± 1.3 (n = 14), but the difference was not statistically significant ($p = 0.18$).

Discussion

It is a well established principle that certain chemicals and drugs may produce male-mediated effects on offspring (7). Furthermore, when such effects have been observed in man, they usually have been seen in other mammals as well (7). In the present study, to test the hypothesis that enflurane adversely affected male reproductive organs, we exposed mice to a concentration of enflurane far above that to which operating room personnel would be exposed. Yet, even

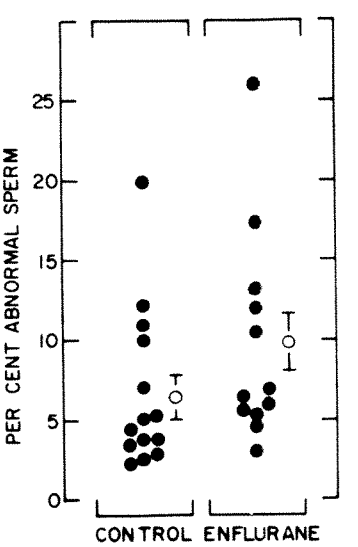


FIG 3. Percentage of morphologically abnormal sperm in mice exposed to enflurane for 18 months. Mean abnormality rate for enflurane-exposed mice was 9.4 ± 1.7 (n = 12) and for control mice, 6.5 ± 1.3 (n = 14).

after 78 weeks of exposure, no damage to reproductive organs could be detected. In particular, histologic examination of the testes showed that enflurane had no effect on spermatogenesis. By contrast, nitrous oxide has been shown to be a powerful suppressor of spermatogenesis in rats. Kripke and colleagues (4) demonstrated that after only 2 days of exposure to 20% nitrous oxide for 8 hours/day, testicular changes could be detected in some LEW/f MAI rats; after 14 days of treatment, all animals were affected. Although, we used a different species of rodent and a different exposure regimen, the contrast between the lack of a testicular reaction to enflurane and the marked changes after nitrous oxide is striking.

The lack of spermatogonial chromosome damage with enflurane can also be contrasted with the effects of chronic exposure to low concentrations of halothane plus nitrous oxide. Coate and colleagues (5) exposed male Sprague-Dawley rats for 7 hours/day, 5 days/week, for 52 weeks, to either halothane, 1 ppm, plus nitrous oxide, 50 ppm, or halothane, 10 ppm, plus nitrous oxide, 500 ppm. Under these conditions, dose-related cytogenetic damage occurred in both bone marrow and spermatogonial cells.

Finally, the failure of enflurane to affect sperm morphology after long-term exposure is at variance with results of a short-term study, previously reported by Land et al (6). In their study, 20 hours of exposure to 1.2% v/v enflurane, significantly increased the percentage of abnormal spermatozoa in (C57Bl/CH3)F_1 mice from 1.4 ± 0.08 (SEM) to 2.04 ± 0.13; exposure to 0.12% v/v enflurane, however, had no effect. The much higher background percentage of abnormalities and higher intragroup variation (6.5 ± 1.3) in Swiss/ICR mice in the present study may be due to a strain difference; more likely, it is the result of the older age of our mice at the time of examination.

Several other approaches have been used to examine enflurane for possible damage to the genome of both somatic and germ cells. These include tests for mutagenicity and for adverse reproductive effects in animals. Of the mutagenicity tests, the Ames *Salmonella*/microsome assay has been used under a variety of conditions and concentrations ranging from 0.1 to 30% v/v (8). Enflurane also has been tested at a concentration of 1.7% in the sister chromatid exchange assay using Chinese hamster ovary cells (9) and at concentrations between 1.5% to 6.5% in the 8-azaguanine test using Chinese hamster lung fibroblasts (10). All three of these mutagenicity assays have given negative results. One study that assessed the effect of enflurane on reproductive performance of male Swiss/ICR mice also was negative (11). No reproductive impairment could be detected in male mice exposed for 4 hours/day, to 1.0% enflurane for 39 days, then to 0.5% for a further 38 days. Thus, to date, the overwhelming evidence indicates that enflurane has no adverse effect on male reproductive organs or on male reproductive processes.

ACKNOWLEDGMENT

Enflurane was a gift from Ohio Medical Products, Madison, Wisconsin.

REFERENCES

1. Askrog V, Harvald B. Teratogenic effects of inhalational anesthetics. Nord Med 1970;83:498–9.
2. Cohen EN, Brown BW, Bruce DL, et al. Occupational disease among operating room personnel: a national study. Anesthesiology 1974;41:321–40.
3. Cohen EN, Brown BW, Wu ML, et al. Occupational disease in dentistry and chronic exposure to trace anesthetic gases. J Am Dent Assoc 1980;101:21–31.
4. Kripke BJ, Kelman AD, Shah NK, Balogh K, Handler AH. Testicular reaction to prolonged exposure to nitrous oxide. Anesthesiology 1976;44:104–13.
5. Coate WB, Kapp RW, Lewis RT. Chronic exposure to low concentrations of halothane-nitrous oxide: reproductive and cytogenetic effects in the rats. Anesthesiology 1979;50:310–8.
6. Land PC, Owen EL, Linde HW. Morphologic changes in mouse spermatozoa after exposure to inhalational anesthetics during early spermatogenesis. Anesthesiology 1981;54:53–6.
7. Soyka LF, Joffe JM. Male mediated drug effects on offspring. In: Schwarz RH, Yaffe SJ, eds. Drug and chemical risks to the fetus and newborn. New York: Alan R Liss, Inc, 1980:49–66.
8. Baden JM, Kelley MJ, Wharton RS, Hitt BA, Simmon VF, Mazze RI. Mutagenicity of halogenated ether anesthetics. Anesthesiology 1977;46:346–50.
9. White AE, Takehisa S, Eger EI, Wolff S, Steven WC. Sister chromatid exchanges induced by inhaled anesthetics. Anesthesiology 1979;50:426–30.
10. Sturrock JE. No mutagenic effect of enflurane on cultured cells. Br J Anaesth 1977;49:777–9.
11. Wharton RS, Mazze RI, Wilson BA. Reproductive and fetal development in mice chronically exposed to enflurane. Anesthesiology 1981;54:505–10.

ANESTH ANALG
1982;61:23-7

Evaluation of the Analgesic Effect and Urinary Excretion of Systemic Bupivacaine in Man

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FRIEDMAN, G. A., ROWLINGSON, J. C., DIFAZIO, C. A., AND DONEGAN, M. F.: Evaluation of the analgesic effect and urinary excretion of systemic bupivacaine in man. Anesth Analg 1982;61:23-7.

Bupivacaine was infused intravenously into healthy volunteers to assess its analgesic effect. In a double-blind manner, 11 male subjects received, on separate days, saline solution or 0.1% bupivacaine, at three rates of infusion. Experimental pain was produced by the tourniquet-induced ischemia test. Times to onset of ischemic pain (threshold) and unbearable pain (tolerance) were compared. Venous blood samples were analyzed for levels of bupivacaine and its metabolite, pipecolyxylidine, by gas chromatography. No significant difference in pain threshold or tolerance was found following control and bupivacaine infusion. In the 72-hour postinfusion urine collection period, only 0.7% of the infused dose was recovered as unmetabolized bupivacaine, with 4.8% recovered as pipecolyxylidine. Systemic blood levels of bupivacaine achieved during regional anesthesia did not produce analgesia in this model.

Key Words: ANESTHETICS, Local: bupivacaine.

INTRAVENOUSLY administered local anesthetic drugs have been reported to produce analgesia and to be useful adjuncts to general anesthesia. Procaine and lidocaine, for example, have been used extensively to supplement nitrous oxide anesthesia. Lidocaine has been shown to decrease anesthetic requirement (MAC) for nitrous oxide in animals and in man (1). However, Rowlingson et al (2) using the submaximal tourniquet ischemia test of Smith and Beecher (3), showed in man that intravenous lidocaine produced only sedation, not analgesia. Bupivacaine also decreases the anesthetic requirement of cyclopropane in rats, but unlike lidocaine, does not produce sedation (4). The purpose of this study was to determine whether systemic levels of bupivacaine achieved in regional anesthesia produce analgesia and to quantitate the urinary excretion of bupivacaine and its metabolite, pipecolyxylidine (PPX), after large doses of bupivacaine.

Methods

Eleven healthy young adult male volunteers weighing 78.3 ± 7.1 (SD) kg with no history of neurologic or vascular disease were studied. Informed consent was obtained from every subject and the protocol was approved by the Committee on Human Experimentation. The submaximal tourniquet ischemia test of Smith and Beecher (3) was used to produce experimental pain. Exsanguination of an upper extremity was achieved by the application of an Esmarch bandage and maintained by inflation of a tourniquet on the upper arm to 250 torr. After 1 minute of ischemia, the subject was asked to squeeze a hand-held rubber ball at the rate of one compression per second for 60 seconds. The arm was then placed at the side of the supine subject and the time from inflation of the tourniquet to the onset of pain (threshold) and unbearable pain (tolerance) were recorded with a stopwatch. Using a table of random numbers to decide the sequence of administration, subjects received either a saline solution or bupivacaine 0.1% in lactated Ringer's solution intravenously in a double-blind manner on 2 separate days, which were at least 3 days

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Supported by a grant from Breon Laboratories, Inc.
Received from the Departments of Anesthesiology, Duke University Medical Center, Durham, North Carolina; University of Virginia Medical Center, Charlottesville, Virginia; and Virginia Baptist Hospital, Lynchburg, Virginia. Accepted for publication September 16, 1981.
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apart. The electrocardiogram (ECG) was monitored continuously. Blood pressure was measured in all subjects who became symptomatic. At least three ischemic trials were performed on each test day before beginning intravenous infusion and served as the control values for that day. A 10- to 20-minute recovery period, during which perfusion of the arm was reestablished after deflation of the tourniquet, preceded the next trial. Following the control trials, a 20-gauge catheter was placed in a vein at the foot or ankle for infusion of the test solution. A 16-gauge catheter connected to a heparin microdrip was placed in the contralateral arm for blood sampling.

A calibrated infusion pump was used to deliver the test solution at three rates. At the beginning of each infusion period a bolus of test solution was given. On the bupivacaine infusion day the bolus consisted of a 12-mg dose, and infusion rates corresponded to 5, 10, and 15 μg/kg/min of bupivacaine in a 70-kg subject. Forty-five minutes after the start of each infusion period, the first ischemic trial was performed. Infusion was continued during the subsequent recovery period during which a 5-ml venous blood sample was obtained. Another ischemic trial was then completed and the plasma level of bupivacaine increased by giving the priming dose and using the next infusion rate. Blood was drawn after each of the infusion periods. Subjects received a total of 199 ± 29 (SD) mg over the course of the infusion. All blood samples were analyzed for bupivacaine by gas chromatography. All urine for each subject was collected for 72 hours following the infusion in six 12-hour collection periods. Each urine specimen was refrigerated immediately after being collected and subsequently analyzed for bupivacaine and its metabolite, PPX.

The values for threshold and tolerance times for the bupivacaine preinfusion ischemic tests, as well as the three infusion test trials, were compared with the values obtained during the corresponding trial on the saline infusion day. The statistical significance of differences between the bupivacaine and saline data were determined using the two tailed paired t-test.

Results

The 11 subjects exhibited wide variations in bupivacaine blood concentrations resulting from the same infusion rate. The subjects, therefore, were divided into three groups based on the blood level of bupivacaine observed: Those with low blood levels (0.1 to 0.7 μg/ml), those with moderate levels (0.8 to 1.3 μg/ml), and those with high levels (1.4 to 1.8 μg/ml). The times to threshold and tolerance of the preinfusion trials on subsequent days were not significantly different, demonstrating the reproducibility of the test. A trend toward increased pain thresholds was observed at all levels but was statistically significant only when blood levels of bupivacaine were in the moderate range ($p < 0.01$) (Fig 1). There was no significant change in tolerance compared with control values for the tourniquet-induced ischemic pain with any of the bupivacaine blood levels achieved (Fig 2).

The data were divided into two groups: those subjects who showed central nervous system (CNS) symptoms during bupivacaine infusion and those that did not (Figs 3 and 4). The asymptomatic subjects showed no significant difference in threshold or tolerance with bupivacaine. The symptomatic subjects, however, tended to demonstrate an increase in pain threshold and tolerance at every bupivacaine blood level when compared with the corresponding test in the control period. This was statistically significant in the moderate blood level threshold group ($p < 0.05$). These symptomatic subjects exhibited wider variation

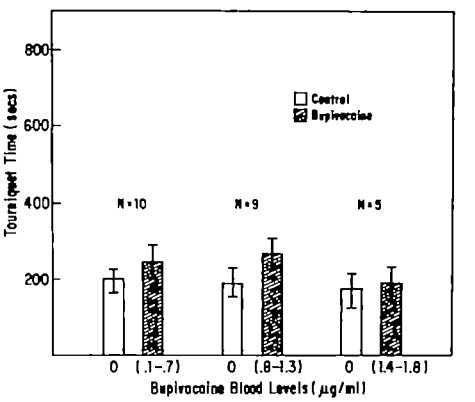


FIG 1. Pain threshold (mean ± 1SD) in subjects with moderate blood levels of bupivacaine were significantly higher than in control patients ($p < 0.01$).

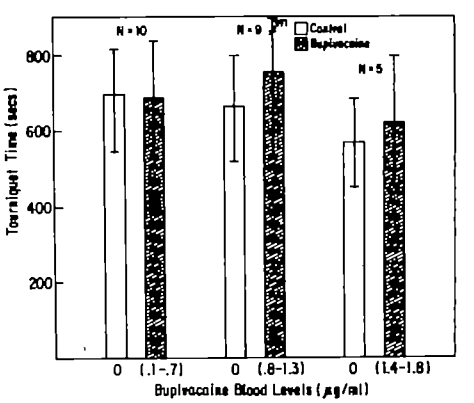


FIG 2. Pain tolerance (mean ± 1SD) in subjects at different blood concentrations of bupivacaine.

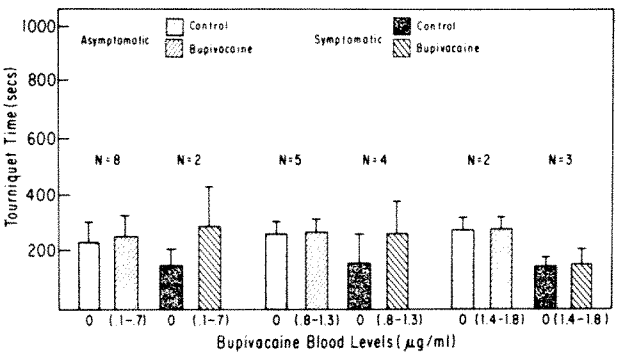


FIG 3. Pain threshold (mean ± 1SD) in subjects who reported central nervous system symptoms are compared with those who remained asymptomatic.

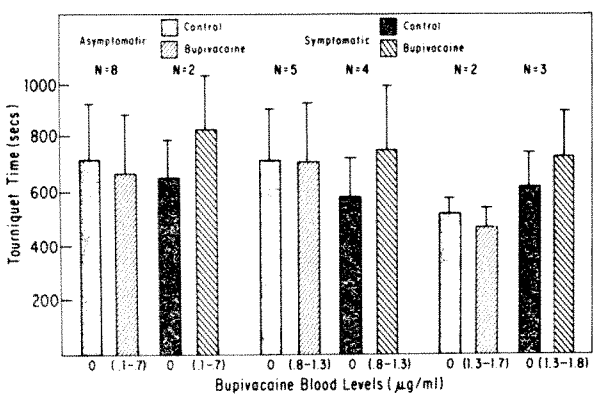


FIG 4. Pain tolerance (mean ± 1SD) in subjects with central nervous system symptoms is compared with those who remained asymptomatic.

in pain threshold and tolerance than did the asymptomatic ones. Interestingly, the subjects who became symptomatic had a significantly decreased pain threshold observed during the preinfusion trials compared with the subjects who remained asymptomatic ($p < 0.025$, utilizing the Mann-Whitney-Wilcoxon 2-tailed test, Fig 5. Pain tolerance was also decreased but not significantly. This trend of decreased pain threshold during placebo infusion in subjects who later developed symptoms was consistently seen during the study (Figs 3 and 4).

With increasing blood levels, the subjects demonstrated a variety of symptoms. With low blood levels, two of 10 subjects reported symptoms; these included facial "tightness" and numbness, tinnitis, and a "rush" sensation. With moderate blood levels, four of nine subjects were symptomatic. Symptoms included drowsiness, weakness, tinnitis, increased auditory perception, headache, nausea, tremor, and scotomata. With high blood levels, three of the five subjects were symptomatic. One subject developed dizziness and tremors and was given 5 mg of diazepam

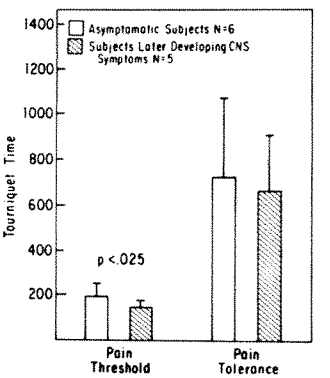


FIG 5. Pain threshold and tolerance (mean ± 1SD) measured during preinfusion control periods are compared between subjects who later developed central nervous system symptoms and those that remained asymptomatic.

intravenously. Within minutes, the trembling decreased and then disappeared over the next 30 minutes. It is interesting to note that the subject with the highest blood level (1.8 μg/ml) was totally asymptomatic. One subject developed scotomata with blood levels of bupivacaine less than 0.1 μg/ml. Only two of the 11 subjects complained of drowsiness or sleepiness. None showed signs of sedation. None of the subjects experienced symptoms during the saline infusion.

No major drug-induced complications were encountered in the study. The continuous ECG revealed no abnormalities in any of the subjects. Blood pressure was measured and found to be in the normal range in all subjects who were symptomatic.

The chromatographic analysis of the urine collected for 72 hours after bupivacaine infusion showed that only 0.7% of the bupivacaine was excreted unchanged and 4.8% was excreted as the metabolite PPX. These were excreted maximally in 12 to 24 hours following infusion (Fig 6). Mean urinary pH in all subjects was 6.1 ± .3.

Discussion

Local anesthetic drugs have been used safely as adjuncts to general anesthesia and there have been several reports of postoperative analgesia subsequent to such use. DeClive-Lowe et al (5) stated that 90% of surgical patients given intravenous lidocaine during surgery had postoperative analgesia and suggested a central sedative effect of the drug. Bartlett and Hutaserani (6) compared postoperative analgesic requirements and subjective pain scores in 600 patients, half of whom had received an anesthetic supplemented with intravenous lidocaine. During the first 24 hours after the operation, 83% of the patients receiving

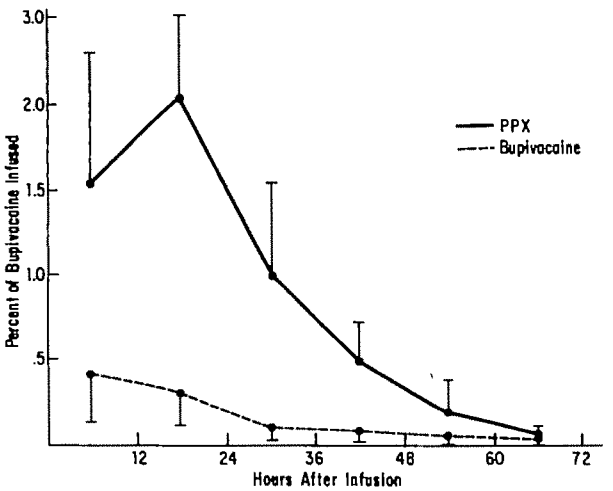


FIG 6. Amount of bupivacaine and its metabolite, pipecolyxylidine, obtained in urine in each 12-hour collection period as percentage of total amount of bupivacaine infused.

lidocaine complained of little or no pain compared with 25% of the control patients.

Lidocaine in blood levels up to 3 μg/ml decreases anesthetic requirement for nitrous oxide requirement in man and animals (1). However, Rowlingson et al (2), in a double-blind study using a tourniquet-ischemic model in man, found that lidocaine at these blood levels produced sedation but not analgesia. Anesthetic requirement, likewise, has been shown to be decreased by systemic infusions of bupivacaine in rats at blood levels that do not produce sedation in the unanesthetized animal (4).

The submaximal tourniquet-induced ischemic test has been shown to identify dependably analgesia produced by a variety of analgesics including morphine and aspirin (3, 7, 8). The pattern of response after administration of an analgesic is a mild increase in threshold with a maximal increase in tolerance after drug administration. This pattern was not seen at any of the blood levels of bupivacaine observed in the present study.

Side effects occurred more frequently as blood levels increased. Subjects exhibiting CNS symptoms generally had an increased threshold and tolerance for pain compared with control subjects, but exhibited wide variation in this respect. The variability of both the symptoms and the blood levels at which they occurred were striking. The two subjects who had the largest increases in threshold and tolerance in the low and moderate blood level groups never achieved high bupivacaine blood levels, and so their influence on the data was absent in the high group. This explains the apparent absence of a dose-response analgesic effect. The increased pain threshold and tolerance seen only in subjects with CNS symptoms implies a central site of action. Perhaps the most interesting finding in this study is the significantly decreased pain threshold observed during the preinfusion control trials in the subjects who later developed CNS side effects with bupivacaine. The sample size is small, however, and further studies will be required to substantiate this conclusion.

In this study subjects received a large dose of bupivacaine, but only a small amount could be accounted for as either parent compound or metabolite in urine, an amount somewhat less than that previously reported by others. Using considerably smaller doses and collecting urine from subjects in whom urine pH was maintained at pH 5, Reynolds (9) recovered 6% of an administered dose as bupivacaine and 5% as PPX in a 24-hour period. The recovery in this study of 0.7% of the administered dose as bupivacaine may have been the result of variation in urinary pH. In our subjects, mean urine pH was 6.1 and the finding of increased excretion with a lower urine pH has been observed by Eriksson and Granberg (10) for similar amide local anesthetics such as lidocaine and prilocaine. PPX excretion seen in this study is almost identical with that reported by Reynolds and suggests that its urinary excretion may not be pH dependent.

In summary, prodromal symptoms appear in some but not all patients with bupivacaine blood levels below the seizure threshold. No cardiovascular effects were seen at blood levels less than 1.8 μg/ml. The findings of this study suggest that systemic bupivacaine blood levels achieved in regional anesthesia (11), i.e., less than 1 μg/ml, do not produce analgesia. A tendency toward an analgesic effect was suggested in some of the subjects who exhibited CNS side effects.

ACKNOWLEDGMENTS

The authors wish to thank Carol Marks and Pat Cannon for their assistance in the typing of this manuscript.

REFERENCES

1. Himes RS Jr, DiFazio CA, Burney RG. Effects of lidocaine on the anesthetic requirements for nitrous oxide and halothane. Anesthesiology 1977;47:437–40.
2. Rowlingson VC, DiFazio CA, Foster J, Carron H. Lidocaine as an analgesic for experimental pain. Anesthesiology 1980;52:20–2.
3. Smith GM, Beecher HK. Experimental production of pain in man: sensitivity of a new method to 600 mg of aspirin. Clin Pharmacol Ther 1969;10:213–6.
4. Neiderlehner JR, DiFazio CA, Foster VA. Comparative general

anesthetic potency and therapeutic index of bupivacaine and lidocaine. Reg Anesth (in press 1981).
5. DeClive-Lowe SG, Gray PWS, North J. Succinyldicholine and lignocaine by continuous drip. Anaesthesia 1954;9:96–104.
6. Bartlett EE, Hutaserani O. Xylocaine for the relief of postoperative pain. Anesth Analg 1961;40:296–304.
7. Williams MW. Ischemic arm pain and non-narcotic analgesics. Toxicol Appl Pharmacol 1959;1:590–7.
8. Smith GM, Egbert LD, Markowitz RA, Mosteller F, Beecher HK. An experimental pain method sensitive to morphine in man: the submaximal effort tourniquet technique. J Pharmacol Exp Ther 1966;154:324–32.
9. Reynolds F. Metabolism and excretion of bupivacaine in man: a comparison with mepivacaine. Br J Anaesth 1971;43:33–6.
10. Eriksson E, Granberg P. Studies on the renal excretion of citanest and xylocaine. Acta Anaesthesiol Scand 1965;Suppl 16:79–5.
11. Moore DC, Balfour RI, Fitzgibbons D. Convulsive arterial plasma levels of bupivacaine and the response to diazepam therapy. Anesthesiology 1979;50:454–6.

Natural History of Chronic Second-Degree AV Nodal Block

This report details experience with documented chronic second-degree atrioventricular (AV) nodal block (proximal to His [H]) in 56 patients. There were 46 men (82%) and 10 women (18%), aged 18 to 87 years. Of the 56 patients 19 (34%) had no organic heart disease (including seven trained athletes) and 37 (66%) had organic heart disease. ECGs in all patients demonstrated episodes of type I second degree block; five patients also had periods of 2:1 block. Prospective follow-up of patients with no organic heart disease (157 to 2280 days, mean 1395 ± 636 days) revealed one patient with clear indication for permanent pacing because of bradyarrhythmic symptoms (permanently paced on day 220 of follow-up). In patients with organic heart disease (prospective follow-up of 60 to 2950 days, mean 1347 ± 825 days), pacemakers were implanted in 10 patients, primarily for treatment of congestive heart failure in eight and syncope in two. Sixteen patients died—three suddenly, seven with congestive heart failure, two of an acute myocardial infarction, and four of causes unrelated to cardiac disease. In summary, chronic second-degree AV nodal block has a relatively benign course in patients without organic heart disease. In patients with organic heart disease, prognosis is poor and related to the severity of underlying heart disease. *(Strasberg B, Amat-Y-Leon F, Dhingra RC, et al: Natural history of chronic second-degree atrioventricular nodal block. Circulation 1981;63:104–9)*

ANESTH ANALG
1982;61:28-31

Surface Landmarks for Supraclavicular Block of the Brachial Plexus

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DUPRE, L.-J., DANEL, V., LEGRAND, J.-J., AND STIEGLITZ, P.: Surface landmarks for supraclavicular block of the brachial plexus. Anesth Analg 1982;61:28-31.

In 136 cases of brachial plexus block using as surface landmarks the external jugular vein, the sternocleidomastoid muscle, and the clavicular insertion of the trapezius muscle, a high success rate and improved safety were noted.

Key Words: ANESTHETIC TECHNIQUES: regional, brachial plexus; ANATOMY: brachial plexus.

BRACHIAL plexus blocks are frequently used for surgery on the upper extremities, particularly in emergency operations. Common techniques for brachial plexus block include axillary (1), infraclavicular (2, 3), supraclavicular (4), and interscalene (5) approaches. The supraclavicular approach has several advantages including the fact that abduction of the arm is not required as with the axillary approach. Furthermore, it is not difficult to block C-8 or T-1, and the local anesthetic solutions cannot spread inside the epidural or subarachnoid spaces, as has been reported with the interscalene technique (6, 7). Pneumothorax is, however, a possible complication of the supraclavicular approach. The incidence of pneumothorax following supraclavicular block averages 0.5% to 6.0% (8), decreasing with experience.

Since the first description of the supraclavicular approach by Kulenkampff and Persy (4) in 1911, many improvements have been suggested, including those by MacIntosh and Mushin (9), Lamoureux and Bourgeois-Gavardin (10), Winnie and Collins (11), and more recently Vongvises and Panijayamond (12). Whatever the technique, three points continue to be a source of concern, especially for neophytes: (*a*) the subclavian arterial pulse can often be felt but the artery cannot always be located accurately, (*b*) if the first introduction of the needle does not elicit paresthesias, while seeking the first rib the needle can slip over it and pierce the pleura and lung parenchyma, and (c) the 22-gauge, 4- or 5-cm-long needle currently so often used is too long to be used so near the pleura.

To avoid these problems we have developed a technique based on readily recognized surface landmarks (13) and now report our experience with 136 cases.

Anatomic Considerations

The supraclavicular fossa or posterior cervical triangle (14) consists of the area enclosed by the posterior margin of the sternocleidomastoid muscle, the middle third of the clavicle, and the anterior edge of the trapezius muscle. The subclavian artery and the trunks of the brachial plexus lie on the floor of the triangle.

The brachial plexus is formed by the anterior roots of the fifth, sixth, seventh, and eighth cervical and first thoracic spinal nerve with occasional twigs from the fourth cervical and second thoracic nerves. The roots emerge between the anterior and middle scalene muscles in the lower part of the posterior triangle of the neck to unite and form three trunks (upper, middle, and lower). As these branches pass downward and laterally behind the clavicle, they are assembled into cords (lateral, medial, and posterior) which divide into the great nerves of the upper extremities.

Using a cadaver placed in the proper position for a supraclavicular block, we observed, after dissection and retraction of the platysma (Fig 1) that a line drawn between the internal clavicular insertion of trapezius

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Received from the Département d'Anesthésie-Réanimation and Laboratoire d'Anatomie, C.H.U. de Grenoble, 38700 La Tronche, France. Accepted for publication September 7, 1981.
Reprint requests to Dr. Dupre, Département d'Anesthésie-Réanimation, C.H.U. de Grenoble; 38700 La Tronche, France.

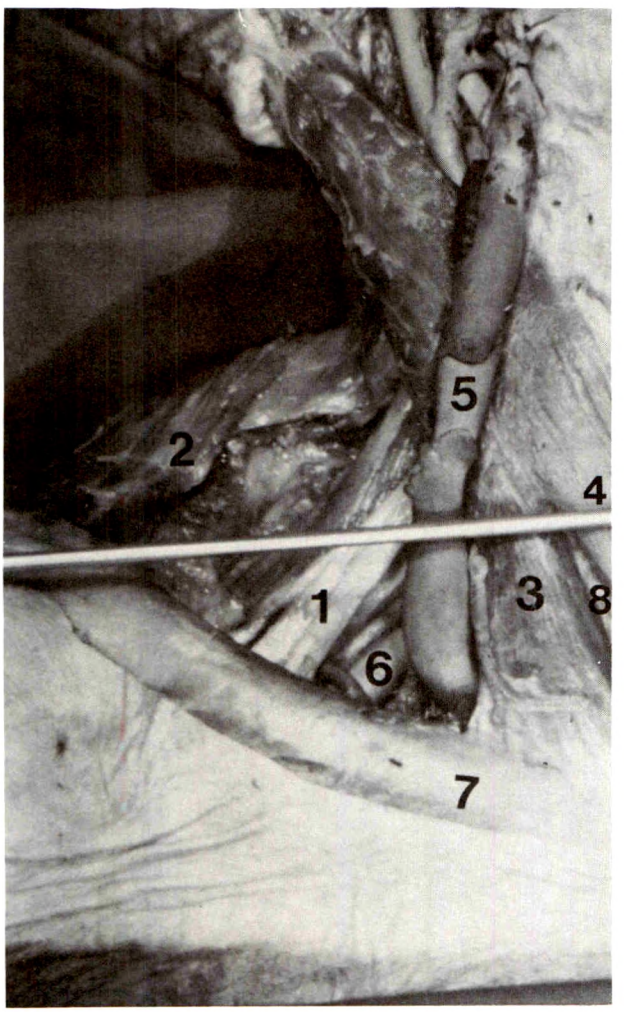


FIG 1. Anatomy. 1, brachial plexus; 2, trapezius muscle; 3, clavicular head; 4, sternal head (3 and 4 comprise the sternocleidomastoid muscle); 5, external jugular vein; 6, subclavian artery; 7, clavicle; 8, fossa supraclavicularis minor.

muscle and the top of supraclavicular minor fossa (15) (the triangle formed by clavicle and the clavicular and sternal heads of sternocleidomastoid muscle) crosses the external jugular vein just in front of the brachial plexus. To be more precise, the brachial plexus lies under the skin at a depth of 1 or 2 cm slightly lateral to the perpendicular projection of the crossing point. These anatomic findings suggest that surface landmarks consisting of the external jugular vein, the sternocleidomastoid muscle, and the clavicular insertion of the trapezius muscle can be used for supraclavicular blocks of the brachial plexus.

Technique

Position

The patient lies in the dorsal recumbent position with a small pillow under the head. The head is turned in the opposite direction, with the arm resting at the side.

Landmarks

The patient is instructed to raise his head, bringing the clavicular and sternal heads of sternocleidomastoid muscle into view. The location of the top of the supraclavicularis minor fossa is marked on the skin with ink. The anesthesiologist moves his index finger laterally along the upper board of clavicle until the internal clavicular insertion of the trapezius muscle is palpated. This point is marked with ink. A line is drawn on the skin, between the two points. Trendelenburg's position or asking the patient to cough helps locate the external jugular vein. An "X" is marked at the intersection of the vein with the previously traced line (Fig 2).

Procedure

After aseptic preparation of the area, the anesthetist, standing at the head of the table, makes a skin wheal at the X mark. A 23-gauge, 2.5-cm needle fitted to a syringe filled with local anesthetic solution is inserted through the skin wheal and advanced slowly caudad, slightly lateral and forward, avoiding puncture of the external jugular vein. All along this insertion, the operator's hand should rest upon the auricle of the ear (Fig 3). When a paresthesia is elicited, local anesthetic solution consisting of 15 to 20 ml of lidocaine 1% mixed with 15 to 20 ml of bupivacaine 0.5% is injected after careful aspiration. If no paresthesia is elicited, redirection and reinsertion of the needle is attempted, but never with a needle longer than 2.5 cm in length.

Results

In our department, 136 blocks using "surface's landmarks" have been performed in 18 months for emergency surgery of the upper extremities. Among the 11 practitioners or students participating in this series, only one had previous experience with plexus blocks. Paresthesias were obtained in all of our patients. General anesthesia was administered to three patients with unsuccessful blocks. In nine cases, the extent of anesthesia was not complete, requiring block of the ulnar nerve (five cases) or the median nerve (two cases). In the two other cases, the medial antibrachial cutaneous nerve was not anesthetized. In three cases, anesthesia was supplemented with small doses of fentanyl (0.1 to 0.2 mg). All the other patients (89%) had complete sensory and motor block of

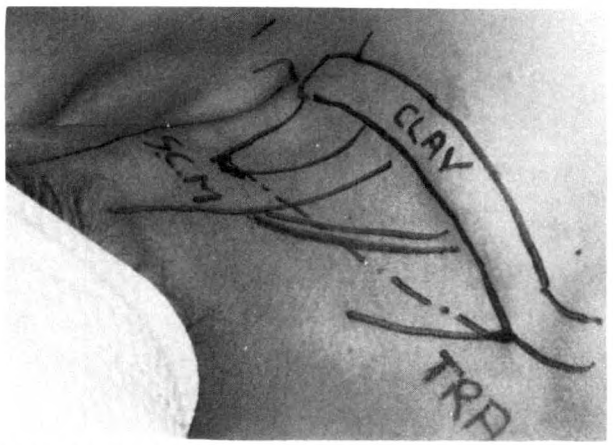


FIG 2. Surface landmarks. From top of supraclavicular fossa [triangle formed by clavicle (CLAV) and the two heads of sternocleidomastoid muscle (SCM)] a line is drawn down to edge of external clavicular insertion of trapezius muscle (TRA). Where this line intersects with external jugular vein "X" is drawn.

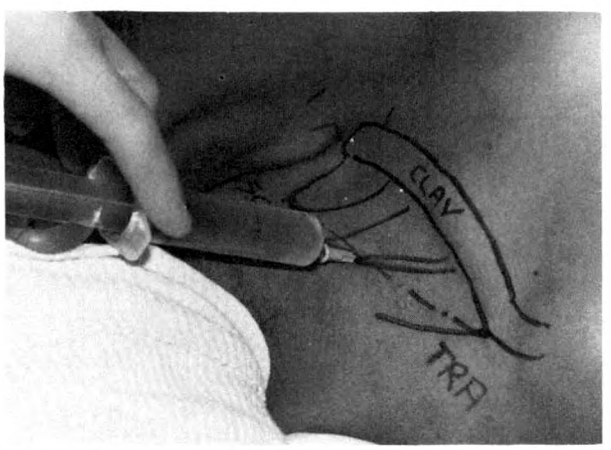


FIG 3. Placement and direction of needle. Inserting needle, operator's hand rests upon auricle of ear. CLAV, Clavicle; TRA, trapezius muscle; SCM, sternocleidomastoid muscle.

brachial plexus. Complications included 12 instances of Horner's syndrome. One patient complained of persistent paresthesias for 3 days after surgery. There were no pneumothoraces.

Discussion

Using the landmarks described above, no pneumothorax was observed in 136 cases and the rate of failure of the blocks performed by inexperienced anesthesiologists was only 2.2%. In a previous series of 217 brachial plexus blocks by experienced practitioners, using the supraclavicular approach described by Moore (8), there was a failure rate of 8.1% and a 1.5% incidence of pneumothorax (16).

The use of short needles even in obese patients may explain the absence of pneumothorax. Yasuda et al (17) suggested inserting needles no more than 3 cm below the skin. Moore (8) recommends using a rubber marker set 2.5 cm from the point of the needle. The best solution is not to use needles longer than 2.5 cm. Besides, our technique avoids the practice of "walking" the rib.

Our landmarks are superficial and easily located just under the skin. They do not require, as with other current techniques, location of the subclavian artery, a relatively deep landmark, deeper than the plexus as shown on Fig 1.

Are our landmarks reliable? The sternocleidomastoid and trapezius muscles have no important anatomic variations, which is not true of the external jugular vein. However, although there are many variations in the origin and the termination of this vein, the part involved in our landmarks seems to be quite consistent (18). Other authors (2, 8, 9) have advocated use of the jugular vein as a landmark. Using these landmarks, paresthesias have been always elicited, a necessity for a high success rate (8, 11).

REFERENCES

1. Hirschel G. Die Anasthesierung des Plexus Brachialis hei operationen an der oberen Extremität. Muench Med Wochenschr 1911;58:1555-6.
2. Pauchet V, Sourdat P, Labat G. L'anesthésie régionale. 3rd ed. Paris: Doin, 1921:153-6.
3. Raj PP, Montgomery SJ, Nettles D, Jenkins MT. Infraclavicular brachial plexus block—a new approach. Anesth Analg 1973;52: 897-904.
4. Kulenkampff D, Persy MA. Brachial plexus anesthesia: its indications, technic and dangers. Ann Surg 1928;87:883-91.
5. Winnie AP. Interscalene brachial plexus block. Anesth Analg 1970;49:455-66.
6. Kumar A, Battit GE, Froese AB, Long MC. Bilateral cervical and thoracic epidural blockade complicating interscalene brachial plexus block: report of two cases. Anesthesiology 1971;35:651-2.
7. Ross S, Scarborough CP. Total spinal anesthesia following brachial plexus block. Anesthesiology 1973;39:458.
8. Moore DC. Regional block: a handbook for use in the clinical practice of medicine and surgery. 4th ed. Springfield, IL: Charles C Thomas, 1975:221-42.
9. MacIntosh RR, Mushin WW. Local anaesthesia: brachial plexus. Oxford: Blackwell Scientific Publications, 1944:56.
10. Lamoureux L, Bourgeois-Gavardin M. La Théorie des trois perpendiculaires dans l'infiltration du plexus brachial. Union Med Can 1951;80:927-34.
11. Winnie AP, Collins VJ. The subclavian perivascular technique of brachial plexus anaesthesia. Anesthesiology 1964;25:353-63.
12. Vongvises P, Panijayanond T. A parascalene technique of brachial plexus anesthesia. Anesth Analg 1979;58:267-73.
13. Dupre LJ, Danel V. Nouveaux repères pour le bloc du plexus brachial par voie supraclaviculaire lavec une série clinique de 44 cas). Anesth Anal Reanim 1980;37:727-9.
14. Anson BJ, McVay CB. Surgical anatomy. Tome 1. 5th ed. Philadelphia: WB Saunders, 1971:304-13.
15. Sobotta J. Atlas d'anatomie humaine. Tome 1. 17th ed. Munich: Urban & Schwarzenberg, 1977:168-9.
16. Dupre LJ, Guillaume F, Nandan RM, Danel V. Six cent treize

anesthésies loco-régionales pendant la garde chirurgicale. Anesth Anal Reanim 1980;37:685–7.
17. Yasuda I, Hirano T, Ojima T, Ohhira TV, Keneko T, Yamamuro M. Supraclavicular brachial plexus block using a nerve stimulator and an insulated needle. Br J Anaesth 1980;52:409–11.
18. Von Lanz T, Wachsmuth W. Praktische anatomie. Berlin: Springer Verlag, 1955:78–81.

Effect of Local Anesthetic Agents on Cardiac Conduction and Contractility

The direct effects of tetracaine, bupivacaine, etidocaine, lidocaine, mepivacaine, and prilocaine were investigated, using an isolated rabbit heart preparation. All of the agents produced a concentration-related depression of intra-atrial, A-V nodal, intraventricular conduction, and myocardial contractility. The more potent local anesthetic agents depress cardiac conduction and contractility at significantly lower concentrations than the less potent local anesthetic drugs. The A-V node appears to be more resistent to the depressant effects of the local anesthetic agents than the atrial and ventricular conduction pathways. In general, the degree of myocardial depression produced by the various drugs is related to their relative local anesthetic potency as determined on an isolated nerve. Tetracaine is the most potent drug in terms of inhibition of nerve conduction and is also the most potent depressant of cardiac conduction and contractility. *(Block AB, Covino BG: Effect of local anesthetic agents on cardiac conduction and contractility. Regional Anesth 1981;6:55–61)*

Transthoracic Resistance in Human Defibrillation

Successful defibrillation depends on delivery of adequate electrical current to the heart; one of the major determinants of current flow is transthoracic resistance (TTR). To study the factors influencing TTR, data were prospectively collected from 44 patients undergoing emergency defibrillation. Shocks of 94 to 450 J delivered energy were administered from specially calibrated Datascope defibrillators that displayed peak current flow, thereby permitting determination of TTR. Shocks were applied from standard (8.5-cm diameter) or large (13 cm) paddles placed anteriorly and laterally. First-shock TTR ranged from 15 to 143 Ω. There was a weak correlation between TTR and body weight ($r = 0.45$, $p < 0.05$) and a stronger correlation between TTR and chest width ($r = 0.80$, $p < 0.01$). Twenty-three patients who were defibrillated using standard 8.5-cm paddles had a mean TTR of 67 ± 36 (SD) Ω, whereas 21 patients who received shocks using paddle pairs with at least one large (13 cm) paddle had a 21% lower TTR of 53 ± 24 Ω ($p = 0.05$). Ten patients received first and second shocks at the same energy level; TTR declined only 8%, from 52 ± 19 to 48 ± 16 Ω ($p < 0.01$). In dogs with closed chest, shocks were administered using a spring apparatus that regulated paddle contact pressure against the thorax. Firmer contact pressure caused TTR to decrease 25%, from 48 ± 22 to 36 ± 17 Ω ($p < 0.01$). Thus, human TTR varies widely and is related most closely to chest size. TTR declines only slightly with a second shock at the same energy level. More substantial reductions in TTR and increases in current flow can be achieved using large paddles and applying firm paddle contact pressure. *(Kerber RE, Grayzel J, Hoyt R, Marcus M, Kennedy J: Transthoracic resistance in human defibrillation: influence of body weight, chest size, serial shocks, paddle size and paddle contact pressure. Circulation 1981;63:676–82)*

ANESTH ANALG
1982;61:32-5

Effects of Intrapartum Maternal Glucose Infusion on the Normal Fetus and Newborn

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MENDIOLA, J., GRYLACK, L. J., AND SCANLON, J. W.: Effects of intrapartum maternal glucose infusion on the normal fetus and newborn. Anesth Analg 1982;61:32-5.

The effect of maternal intravenous glucose infusion on the newborn's glucose, insulin, and neurobehavioral performance was studied prospectively in 56 normal mother-newborn pairs. Maternal blood glucose levels at the time of delivery, umbilical venous blood glucose and insulin levels, and neonatal blood glucose levels were measured. Neurobehavioral assessment of the newborns was performed at 4 and 24 hours of life. The median value for total amount of glucose infused to the mother was 32.5 g, the median rate of glucose infusion was 8 g/h, and the median maternal blood glucose concentration at delivery was 110 mg/dl. Median umbilical venous blood glucose concentrations were 104 mg/dl and median insulin concentration was 15 μU/ml. Six babies were hypoglycemic at 1 hour of age. Umbilical venous glucose and insulin levels correlated significantly ($p < 0.001$) with the rate of glucose infusion to the mother and her blood glucose level. The incidence of neonatal hypoglycemia was significantly related ($p < 0.05$) to a maternal blood glucose level greater than 120 mg/dl, to a glucose infusion rate of 20 g/hr or greater and to an umbilical venous insulin level of greater than 40 μU/ml. There were no major differences in neurobehavior that distinguished hypoglycemic neonates. It is recommended that the normal parturient be given less than 20 g/hr of intravenous glucose before delivery and have a blood glucose level less than 120 mg/dl at the time of delivery. Newborns delivered to mothers with hyperglycemia or excessive glucose infusion should be tested for hypoglycemia at 1 and 2 hours of age.

Key Words: ANESTHESIA: obstetric; METABOLISM: glucose; HORMONES: insulin.

ADMINISTRATION of intravenous fluids containing glucose are a recommended antepartum anesthetic practice (1). Yet, maternal hyperglycemia and fetal hyperinsulism regularly occur in response to an excessive glucose load (2-6). Indeed, in a retrospective study, mothers in labor given intravenous infusions of glucose delivered newborns with lower average blood glucose levels than did mothers not given intravenous glucose (7). The incidence of hypoglycemia, however, was not indicated in that study. Neonatal hypoglycemia can cause acute and long-term morbidity (8), largely neurologic. Because of these factors, we conducted a prospective study to determine the relationships between maternal glucose infusion and fetal and neonatal insulin and blood glucose levels, as well as subsequent neonatal neurobehavior in an otherwise healthy and normal population.

Methods and Patients

Fifty-six mother-newborn pairs were studied after informed consent had been obtained. All pregnancies were at term and without complications. Specifically, no mothers had diabetes or glucosuria of pregnancy or toxemia and there were no cases of intrauterine growth retardation, perinatal asphyxia, maternal hypotension, or bleeding.

Forty-one mothers delivered vaginally and 14 had elective cesarean sections. Of the 41 vaginal deliveries, 29 had epidural, four general, and eight local anesthesia. Of the 14 operative deliveries, six were done with epidural and eight with general anesthesia.

All mothers received intravenous glucose before delivery in accordance with standard practice. The total glucose load and the rate of glucose infusion

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Received from the Departments of Neonatology and Pediatrics, Georgetown University School of Medicine, and Department of Neonatology, Columbia Hospital for Women, Washington, D.C. Accepted for publication September 8, 1981.

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were determined by an attending physician not involved in this study. Venous blood was obtained from the mother at the time of delivery. Umbilical venous blood was obtained from the umbilical cord at delivery.

Blood glucose concentration was determined by the orthotoluidine method (9) (Clinicard, Instrumentation Laboratory, Lexington, MA). Coefficient of variability for this test was ±2.0%. Insulin determinations were done by a radioimmunoassay test system (Immophase, Ames Co, Ames, IA) (10). Coefficient of variability for this test was 6.9%. Dextrostix (Corning Medical Diagnostics, Medfield, MA) tests were performed on every baby at 1, 2½, and 4 hours of age using capillary blood drawn by heelstick. Dextrostix correlate accurately with glucose levels in simultaneously drawn venous blood samples (11). In the present study, a Dextrostix reading less than 45 mg/100 ml was regarded as abnormal. These infants had their blood glucose determined immediately. Any newborn fed before 4 hours of age for any reason other than low blood glucose was eliminated from the study.

Neurobehavioral examination was performed on all babies at 4 and 24 hours of age using the Early Neonatal Neurobehavioral Scale as previously described (12). The neurobehavioral examiner was not aware of glucose and insulin values or of maternal glucose load at the time of testing.

Each infant was examined by pediatricians not involved in this study. All infants were appropriate in length, weight, and head circumference for term gestational age. All were reported normal on pediatric examination.

Statistical analysis used either linear correlation analysis for parametric data or the median chi-square test for nonparametric data (13). Interrelationships between maternal glucose infusion and maternal blood glucose, umbilical vein glucose, and insulin levels were assessed by linear correlation analysis. The relationship between the incidence of hypoglycemia and other significant occurrences was determined by median chi-square analysis.

Results

Maternal Glucose Infusion, Maternal Blood Glucose

The total amount of maternal glucose administered ranged from 3.5 to 82.5 g; median was 32.5 g. Rate of glucose infusion ranged from 0.35 to 57 g/hr; median was 8 g/hr. Median time interval between the start of glucose infusion and delivery was 4.1 hours with a range of 0.7 to 17 hours. Maternal blood glucose levels at delivery had a median of 110 mg/dl with a range of 68 to 230 mg/dl. The total amount of glucose infused correlated significantly ($p < 0.01$) with maternal blood glucose levels.

Cord Blood Glucose and Insulin

Median umbilical vein glucose level was 104 mg/dl with a range of 73 to 215 mg/dl. The correlation coefficient between maternal and umbilical vein glucose levels was $r = 0.94$, $p < 0.001$). Umbilical vein insulin concentrations ranged from 3.1 to 202 μU/ml. The umbilical vein glucose levels correlated significantly ($p < 0.001$) with the total glucose load and the glucose infusion rate. The umbilical vein glucose also correlated significantly with the maternal blood glucose concentration ($p < 0.001$). The umbilical vein insulin level was significantly related to the rate of glucose infusion in the mother ($p < 0.001$) as well as to maternal blood glucose and to umbilical vein glucose ($p < 0.01$). The relationships among maternal glucose concentration, amount, and rate of glucose infusion, and umbilical vein glucose and insulin levels are summarized in Table 1.

Neonatal Hypoglycemia

Six of the 56 babies (11%) had hypoglycemia at 1 hour of age. The presence of low blood glucose in the newborn significantly correlated ($p < 0.05$) with a maternal blood glucose level of 120 mg/dl or greater (Table 2). Furthermore, low neonatal glucose levels correlated ($p < 0.05$) with a maternal glucose infusion

TABLE 1

Relationships among Maternal Infusion Amount and Rate, Maternal Blood Glucose Level, and Umbilical Vein Glucose and Insulin

	Median (range)	MG	UVG	UVI
Glucose amount (GA)	32.5 g (3.5–82.5)	$p < 0.01$	$p < 0.001$	—
Glucose rate (GR)	8 g/hr (35–57)	—	$p < 0.001$	$p < 0.001$
Maternal glucose (MG)	110 mg/dl (68–230)	—	$p < 0.001$	—
Umbilical vein glucose (UVG)	104 mg/dl (73–215)	—	—	$p < 0.01$
Umbilical vein insulin (UVI)	15 μU/ml (3.1–202)	$p < 0.01$	—	—

TABLE 2

Relationships between Neonatal Hypoglycemia and Maternal Glucose Infusion Rate, Maternal Blood Glucose, and Umbilical Vein Insulin Values

	Neonatal hypoglycemia
Maternal glucose infusion rate: ≥20 g/hr	$p < 0.05$
Maternal blood glucose level: ≥120 mg/dl	$p < 0.05$
Umbilical vein insulin level: ≥40 μU/ml	$p < 0.01$

rates of 20 g/hr or greater (Table 2). Neonatal hypoglycemia also correlated significantly ($p < 0.01$) with umbilical vein insulin levels greater than 40 μU/ml (Table 2). Importantly, hypoglycemia in all babies promptly responded to appropriate therapy.

Neurobehavioral Examination

Habituation to auditory stimulus was significantly better ($p < 0.01$) in hypoglycemic neonates than in the nonhypoglycemic neonates at 4 hours of age. There were no other significant differences associated with neonatal blood glucose levels, although in hypoglycemic infants there was a tendency not to extinguish Moro's response and to have poorer rooting at age 4 hours. The predominant sleep-wake state for normoglycemic and hypoglycemic infants was awake (A-2 awake). There were no differences for any neurobehavioral measure at 24 hours of age.

Discussion

The present report demonstrates that parenteral glucose administration to the parturients significantly affects glucose and insulin homeostasis in both mother and fetus and newborn infant. As expected (4, 14), the maternal blood glucose level was directly related to the amount of glucose infused. Although average maternal glucose levels were within normal range, there were several mothers who were hyperglycemic at the time of delivery. The direct correlation between maternal blood glucose levels and umbilical vein glucose levels is also consistent with previous findings (15). This relationship has been suggested to be due to facilitated diffusion of glucose across the placenta (16). In contrast, maternal insulin does not cross the placenta in measureable amounts. In our study, umbilical vein insulin levels correlated significantly with umbilical vein glucose concentration, maternal glucose concentration, and the rate of glucose infusion in the mother. These findings support the hypothesis that the term fetal pancreas can respond to a glucose load by increased insulin release (17). Therefore the cause of neonatal hypoglycemia is maternal hyperglycemia which leads to fetal hyperglycemia and subsequent fetal hyperinsulinemia.

The 11% incidence for hypoglycemia in the present study is slightly higher than that previously reported in term babies (7, 18). These previous reports were based on the finding of a single low blood glucose during the first 6 hours of life. They did not consider the impact of iatrogenic maternal glucose excess, however. In our study, hypoglycemia significantly correlated with maternal glucose infusion rates of 20 g/hr or greater, maternal blood glucose concentrations of more than 120/mg/dl, and umbilical vein insulin levels of greater than 40 μU/ml. These observations suggest that rate of glucose loading as well as peak maternal blood glucose both produce neonatal hypoglycemia. Cornblath et al (7) have shown that in vaginally delivered neonates average blood glucose values were lowest in babies born to mothers given intravenous infusions of glucose during labor. Milner and Hales (2) demonstrated that bolus intravenous glucose administration to the mother produces higher fetal and maternal blood glucose values, but an infusion given over a long period of time causes a greater sustained increased in fetal insulin levels. In that study, evidence of fetal pancreatic response took as long as 60 minutes in some cases.

The results of the neurobehavioral examination done at 4 hours of age showed that hypoglycemic neonates could not be distinguished from normal neonates except by increased auditory habituation, and perhaps by Moro's maneuver extinction. The absence of prominent early neurobehavioral abnormalities is reassuring. However, our experimental design was such that neurobehavioral evaluation was not performed at the exact time of the hypoglycemia (1 hour of age) but at 4 hours of age. By this time, treatment had been given and blood glucose levels had returned to normal. Previous studies (8) have shown that central nervous system effects from neonatal hypoglycemia may occur beyond the period of low blood glucose. The absence of significant behavioral differences at 24 hours of age indicates that long-term neurobehavioral consequences in this population of selectedly normal neonates are remote.

Fetal hyperglycemia may also be potentially harmful to the developing brain. Animal studies have shown that brain content of glucose and related carbohydrates critically influences the brain's tolerance to anoxia. Elevation of serum glucose levels increases the brain's susceptibility to injury by increasing the accumulation of lactic acid in brain tissue during

exposure to anoxia (19). By design, all parturients and all labors in the present study were normal. However, avoidance of hyperglycemia in fetuses with asphyxia may be of even greater importance.

Based on previous studies and the present data, we feel it prudent to avoid excess prepartum intravenous infusion of glucose and thus to avoid maternal and fetal hyperglycemia. Although there is wisdom in the practice of maintaining an intravenous route in all parturients who receive anesthesia, the maternal glucose load and rate of glucose infusion should be monitored and limited. Specifically, we recommend that the rate at which glucose is infused intravenously to mothers before delivery should not exceed 20 g/hr and that maternal blood glucose concentration should not exceed 120 mg/dl at the time of delivery. Furthermore, babies whose mothers received excess parenteral glucose before delivery should be monitored for hypoglycemia during the first 2 hours of life. This is especially important when maternal hyperglycemia has occurred.

ACKNOWLEDGMENTS

The authors acknowledge laboratory support from the Pathology Department at Columbia Hospital under the direction of Dr. William Jaffurs; and secretarial assistance from Dolores Sanders and Carrie Grose.

REFERENCES

1. Marx GF, Shnider SM (ed). The anesthesiologist, mother and newborn. Baltimore: Williams & Wilkins, 1974;86–92.
2. Milner R, Hales C. Effect of intravenous glucose on concentration of insulin in maternal and umbilical cord plasma. Br Med J 1965;1:284–90.
3. Tobin J, Roux J, Soeldner J. Human fetal insulin response after acute maternal glucose administration during labor. Pediatrics 1969;44:668–72.
4. Beard R, Turner R, Oakley N. Fetal response to glucose loading: fetal blood glucose and insulin responses to hyperglycemia in normal and diabetic pregnancies. Postgrad Med 1971;47:68–75.
5. Lind T, Gilmore A, McClarence M. Cord plasma glucose and insulin concentration and maternal-fetal relations. Br J Obstet Gynaecol 1975;82:562–6.
6. Flige A, Kunzel W, Mitzkal H. Fetal and maternal blood glucose insulin and acid base observations following maternal glucose infusion. J Perinat Med 1977;5:84–91.
7. Cornblath M, Ganzon AF, Nicolopoulos D, et al. Studies of carbohydrate metabolism in the newborn infant. III. Some factors influencing the capillary blood sugar and the response to glucagon during the first hours of life. Pediatrics 1961;27: 378–84.
8. Cornblath M, Schwartz R. Disorders of carbohydrate metabolism in infancy, 2nd ed. Philadelphia: WB Saunders, 1976:82–104.
9. Dubowski K. An o-toluidine method for body-fluid glucose determination. Clin Chem 1962;8:215–23.
10. Yalow RS, Berson SA. Immunoassay of endogenous plasma insulin in man. J Clin Invest 1960;39:1157–66.
11. Fox RE, Redstone D. Sources of error in glucose determinations of neonatal blood by glucose oxidase methods, including Dextrostix. Am J Clin Pathol 1976;66:658–61.
12. Scanlon JW, Brown MV, Weiss JB, Alper MH. Neurological responses of newborn infants after maternal epidural anesthesia. Anesthesiology 1974;40:121–31.
13. Siegel S. Non-parametric statistics. New York: McGraw-Hill, 1956:104–11.
14. Cordero L, Grunl J, Anderson G. Hypertonic glucose infusion during labor. Am J Obstet Gynecol 1970;15:560–7.
15. Chinard F, Danecino U, Hartman W, et al. The transmission of hexoses across the placenta in the human rhesus monkey. J Physiol 1956;132:298–305.
16. Barnes AC. Intrauterine development. Philadelphia: Lea & Fabiger, 1968:67–78.
17. Obenshain S, Adam P, King K, et al. Human fetal insulin response to sustained maternal hyperglycemia. N Engl J Med 1970;283:566–9.
18. Lubchenco L, Bard H. Incidence of hypoglycemia in newborn infants classified by birth weight and gestational age. Pediatrics 1971;47:831–7.
19. Myers RE, Myers SE. Use of sedative, analgesic, and anesthetic drugs during labor and delivery: bane or boon? Am J Obstet Gynecol 1979;133:83–104.

ANESTH ANALG
1982;61:36–41

Cuffed Tracheal Tubes—Physical and Behavioral Characteristics

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BERNHARD, W. N., YOST, L., TURNDORF, H., AND DANZIGER, F.: Cuffed tracheal tubes—physical and behavioral characteristics. Anesth Analg 1982;61:36–41.

This study compares physical and behavorial characteristics of currently used cuffed tracheal tubes. Variability in physical and behavioral characteristics between size 8 tracheal tubes and cuffs exists: radius of tube curvature varies from 12.1 to 15.8 cm, bevel angle 39 to 56°, bevel direction 73 to 107°, distance from proximal end of bevel to cuff 15.4 to 24.4 mm, internal tube diameter 7.5 to 8.8 mm, wall thickness 1.14 to 2.37 mm, force to collapse 1020 to 3103 g, angle to kink 52 to 96°, and indentation hardness 65.4 to 83.1. Cuff lengths vary from 29.7 to 45.3 mm, thickness 0.03 to 0.54 mm, diameter 14.5 to 32 mm, and cuff resting volume 0.15 to 19.9 ml. We recommend use of a soft, thermolabile, kink- and collapse-resistant tracheal tube fitted with a soft, thin-walled, tough, compliant, moderately long cuff, with a moderately large resting volume and diameter larger than tracheal diameter. Argyle, National Catheter, Ohio, Portex, Rusch "safety," and Shiley tracheal tubes resist collapse and kinking. Argyle, Lanz, National Catheter "hi-lo," National Catheter "intermediate hi-lo," Ohio, and Portex "profile" cuffs are thin and have diameters larger than the average male tracheal diameter.

Key Words: EQUIPMENT: tracheal tubes, tracheal tube cuffs.

CONCERN over laryngeal and tracheal injury from cuffed tracheal tubes prompted studies to define better the etiology, nature, and extent of cuff and tube trauma (1–4). Interest has centered on lesions produced by high lateral tracheal wall pressure exerted by cuffs rather than injury caused directly by tracheal tubes. A wide variety of lesions and problems directly related to the tube itself have been reported. Among these are hematoma, laceration of mucous membranes, laceration of the vocalis muscle, and arytenoid cartilage subluxation with intubation (5); and tube obstruction, subglottic stenosis, tube displacement, stridor following extubation, nasal ulceration with prolonged intubation in children (6); and hoarseness and upper airway obstruction following extubation in adult patients (7). Controversy over prolonged use of nasotracheal tubes rather than tracheostomy (8–10), complications of translaryngeal intubation (5–11), and need to increase intubation safety prompted our study of physical and behavioral characteristics of currently available cuffed tracheal tubes.

Methods and Materials

The following measurements were made on six samples of 10 types (same lot each type) of size 8 tracheal tubes at 24 C: (*a*) radius of curvature using compass and ruler, (*b*) bevel angle, (*c*) bevel direction using an adjustable protractor (direction bevel facing in patient with tube curvature facing anteriorly), (*d*) distance from proximal end of bevel to distal end of cuff, (*e*) anterior-posterior and lateral-lateral internal diameters (i.d.), and (*f*) tube wall thickness using a vernier caliper. The following measurements were also made on six of 12 types (same lot each type) of cuffs (attached to tubes) at 24 C: (*a*) length and (*b*) diameter at resting volume with a vernier caliper, (*c*) wall thickness with a Mitutoyo micrometer, and (*d*) resting volume with a calibrated syringe (Table 1).

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Received from the Department of Anesthesiology, New York University Medical Center, New York, New York. Accepted for publication September 11, 1981. Presented in part at the Annual Meeting of the American Society of Anesthesiologists, October 1980, St. Louis, Missouri.

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Force required to produce anterior-posterior collapse to 50% of internal diameter (4 mm) was measured at 37 C and 100% relative humidity with an acrylic jig with 5.8-mm contact edge. These measurements were repeated after removal of collapse force for 30 seconds. "Angle to kink" was measured twice at 37 C and 100% humidity after fixing tubes at two points 8 cm apart. Each tube was flexed in the direction of curvature using a worm screw jig until a visible kink or flattening of the tube occurred. A second measurement was done 30 seconds after releasing the initial kink. Indentation hardness of an additional group of tracheal tubes was measured with a type A-2 Shore durometer at 21 and 37 C on platens made from 10 batches of tracheal tubes using ASTM method D 2240-68 (12). Standard deviations (SD) from the mean were determined for each group of measurements.

TABLE 1
Cuffed Tracheal Tubes (8.0 mm)

Tube	Name	Tube material	Cuff material and name	N
Rusch	—	Red rubber	Latex	6
Bivona	—	Silastic	Silastic "airecuff"	6
Portex	"blue line"	PVC*	PVC "profile cuff"	6
Lanz	—	PVC	PVC	6
Shiley	—	PVC	PVC	6
Ohio	—	PVC	PVC	6
Argyle	—	PVC	PVC	6
National Catheter	"hi-Lo"	PVC	PVC "hi-lo"	6
Rusch	"safety"	PVC	PVC "super safety"	2†
Franklin	"softway"	PVC	PVC	6
National Catheter‡	"Intermediate hi-lo"	PVC	PVC	6
Concept (prototype)‡	C-Flex	PVC	?	6

* PVC, Polyvinylchloride.
† Two tubes measured three times for six numbers.
‡ Cuff measurement only.

Results

Radius of curvature varied between 12.05 (Ohio) and 15.78 cm (Rusch "red rubber," RR) (Table 2). Tube tip bevel angle ranged from 39° (National Catheter) to 56° (Rusch RR). All bevels faced left of the curvature axis, but Portex "blue line" and Lanz bevels measured 17° above and Rusch "safety" tube 17° below 90° left. Distance from proximal end of bevel to distal end of cuff varied from 15.4 (Shiley) to 24.4 mm (Rusch "safety"). Internal diameter for 8.0-mm tubes varied between 7.5 (Franklin and Rusch RR) and 8.76 mm (Franklin). Anterior-posterior diameter of Franklin's "softway" tube differed from its lateral diameter by 1.26 mm and Portex blue line was slightly wider in its lateral-lateral dimension (Δ = .54 mm). Tube wall thickness ranged from 1.15 (Lanz) to 2.37 mm (Rusch RR). Difference between thickest and thinnest points was largest on the Rusch red rubber tube (Δ = .74 mm). The Bivona tube contained approximately 40 fine longitudinal ridges.

TABLE 2
Tracheal Tube Physical Characteristics

Cuffed tracheal tube	Radius of curvature	Bevel angle	Bevel direction*	Distance bevel-to-cuff	Internal diameter		Wall thickness	
					A-P	L-L	Minimum	Maximum
	cm	°	°	*mm*	*mm*		*mm*	
Rusch "red rubber" (n = 6)	15.78 ± 1.48	56 ± 1.63	85 ± 3.94 Left	19.0 ± 2.13	7.67 ± 0.20 Δ = 0.17	7.50 ± 0.11	1.63 ± 0.10	2.37 ± 0.28 Δ = 0.74
Bivona (n = 6)	13.95 ± 2.02	46 ± 1.10	80 ± 27.22 Left	20.3 ± 0.82	8.18 ± 0.17 Δ = 0.10	8.08 ± 0.12	1.79 ± 0.07	2.15 ± 0.06 Δ = 0.36
Portex "blue line" (n = 6)	13.57 ± 0.66	42 ± 1.03	107 ± 7.36 Left	20.1 ± 0.90	7.79 ± 0.11 Δ = 0.54	8.33 ± 0.08	1.42 ± 0.01	1.44 ± 0.02 Δ = 0.02
Lanx (n = 6)	13.36 ± 0.73	49 ± 0.98	107 ± 17.50 Left	20.7 ± 0.68	8.37 ± 0.18 Δ = 0.26	8.11 ± 0.15	1.15 ± 0.10	1.41 ± 0.04 Δ = 0.26
Shiley (n = 6)	15.12 ± 0.44	47 ± 1.64	88 ± 13.35 Left	15.4 ± 0.44	7.96 ± 0.14 Δ = 0.17	8.13 ± 0.13	1.44 ± 0.06	1.51 ± 0.05 Δ = 0.07
Ohio (n = 6)	12.05 ± 0.63	52 ± 1.6	88 ± 13.71 Left	19.5 ± 1.14	8.03 ± 0.06 Δ = 0.03	8.00 ± 0.06	1.23 ± 0.03	1.47 ± 0.04 Δ = 0.24
Argyle (n = 6)	13.25 ± 0.59	47 ± 1.47	92 ± 2.23 Left	21.8 ± 0.97	7.82 ± 0.14 Δ = 0.07	7.75 ± 0.19	1.43 ± 0.03	1.48 ± 0.02 Δ = 0.05
National Catheter "hi-lo" (n = 6)	13.07 ± 0.52	39 ± 1.03	89 ± 2.73 Left	16.6 ± 0.78	8.13 ± 0.29 Δ = 0.07	8.06 ± 0.13	1.30 ± 0.03	1.54 ± 0.08 Δ = 0.24
Rusch "safety tube "(n = 2)†	13.60 ± 0.71	49 ± 1.41	73 ± 2.83 Left	24.4 ± 0.71	7.93 ± 0.04 Δ = 0.16	7.77 ± 0.24	1.27 ± 0.03	1.60 ± 0.00 Δ = 0.33
Franklin "softway" (n = 6)	14.3 ± 2.80	43 ± 1.41	94 ± 7.50 Left	19.9 ± 0.77	8.76 ± 0.32 Δ = 1.26	7.50 ± 0.28	1.41 ± 0.05	1.55 ± 0.04 Δ = 0.14

* 90° bevel facing exactly to patient's left.
† Each tube was measured 3 times for 6 numbers.

Force to collapse to 50% of i.d. (4 mm) varied between 1020 (Lanz) and 3103 g (Rusch RR) (Table 3). Franklin "softway" and Lanz tubes collapsed with low force (1047 and 1126 g). Portex blue line had the most memory for collapse (1633 − 1421 = 212 g) (collapse easier the second time) and Franklin softway the least memory (1047 − 1032 = 15 g). The angle at which initial kinking occurred ranged from 52 (Rusch "safety") to 87° (Rusch RR) (Table 3). Lanz (84°) and Franklin (81°) kinked easier than Shiley (79°), Portex "blue line" (77°), Ohio (77°), Argyle (74°), National Catheter "hi-lo" (67°), and Bivona (60°) tubes. Indentation hardness, expressed numerically, varied between 65.4 (Portex) and 76.33 (Argyle) at 37 C (Table 4). Hardness of three different Rusch tubes varied from 71.4 to 75.0 at 37 C. With warming from 21 to 37 C, all hardness reading decreased 5 to 9.4 units (Table 4).

Cuff length varied between 29.7 (Rusch RR) and 45.3 mm (Shiley) (Table 3). Cuff thickness ranged from .537 (latex cuff on Rusch RR tube) to .033 mm (National Catheter "hi-lo" cuff). Cuff diameter varied between 14.5 mm (Rusch RR) to 32 mm (Lanz). Cuff resting volumes ranged from .15 (Rusch RR) to 19.9 ml (Argyle). The latex cuff on the Rusch RR tube was shortest (29.7 mm), thickest (.537 mm), and had the

TABLE 3
Tube Behavior and Cuff Dimensions

Cuffed tracheal tube	Tube behavior		Cuff dimensions			
	Collapse force (A-P)	Kink angle	Length	Thickness	Diameter	Resting volume
	g	°		*mm*		*ml*
Rusch "red rubber" (n = 6)	3103 ± 634 3058 ± 594 Δ = 45	87 ± 3.60 96 ± 4.00 Δ = 9	29.6 ± 1.17	0.537 ± 0.029	14.5 ± 0.44	0.15 ± 1.17
Bivona "aire cuff" (n = 6)	2803 ± 259 2766 ± 267 Δ = 37	60 ± 1.90 78 ± 4.90 Δ = 18	44.6 ± 1.42	0.213 ± 0.004	31.7 ± 1.14	16.9 ± 0.91
Portex "blue line" "profile cuff" (n = 6)	1633 ± 154 1421 ± 145 Δ = 212	77 ± 3.10 87 ± 2.60 Δ = 10	35.1 ± 0.88	0.097 ± 0.004	26.5 ± 0.53	9.9 ± 1.4
Lanz (n = 6)	1126 ± 166 1020 ± 148 Δ = 106	84 ± 2.80 94 ± 2.80 Δ = 10	38.8 ± 1.33	0.084 ± 0.011	32.0 ± 0.42	18.6 ± 0.74
Shiley (n = 6)	1655 ± 212 1489 ± 199 Δ = 166	79 ± 3.20 91 ± 3.40 Δ = 12	45.3 ± 1.20	0.090 ± 0.010	23.2 ± 1.12	9.2 ± 0.40
Ohio (n = 6)	1466 ± 91 1384 ± 68 Δ = 82	77 ± 2.71 82 ± 1.86 Δ = 5	42.5 ± 1.3	0.081 ± 0.008	26.8 ± 0.66	13.0 ± 0.79
Argyle (n = 6)	1784 ± 106 1670 ± 112 Δ = 114	74 ± 1.40 87 ± 4.30 Δ = 13	41.8 ± 0.79	0.069 ± 0.007	30.8 ± 1.22	19.9 ± 0.63
National Catheter "hi-lo" (n = 6)	1897 ± 266 1731 ± 275 Δ = 166	67 ± 2.70 78 ± 4.70 Δ = 11	43.3 ± 1.02	0.033 ± 0.003	29.5 ± 0.97	19.2 ± 1.32
Rusch "safety tube" "super-safety" cuff (n = 2)	1610 ± 288 1474 ± 352 Δ = 136	52 ± 2.80 67 ± 2.10 Δ = 15	40.1 ± 0.93	0.191 ± 0.020	24.7 ± 0.92	12.4 ± 0.49
Franklin "softway" (n = 6)	1047 ± 98 1032 ± 105 Δ = 15	81 ± 3.27 90 ± 2.64 Δ = 9	38.3 ± 0.70	0.268 ± 0.023	17.9 ± 0.95	4.0 ± 0.18
National Catheter "Intermediate hi-lo" (n = 6)			33.6 ± 1.73	0.059 ± 0.017	28.4 ± 0.69	9.9 ± 0.48
Concept "C-Flex" (prototype) (n = 6)			32.1 ± 1.59	0.118 ± 0.028	16.6 ± 0.88	2.4 ± 0.51

* Two tubes measured three times for six numbers

TABLE 4
Tracheal Tube Hardness Readings

Cuffed tracheal tube	No. of readings	Durometer reading	
		21 C	37 C
Portex (n = 2, oral)	10	82.00 ± 1.60	75.70 ± 1.57
Portex (n = 1, nasal)	5	72.80 ± 1.64	65.40 ± 1.82
Lanz (n = 3)	15	81.67 ± 1.05	74.33 ± 1.23
Shiley (n = 3)	15	81.13 ± 1.19	75.40 ± 1.06
Ohio (n = 3)	15	82.13 ± 1.55	75.87 ± 1.41
Argyle (n = 3)	15	83.13 ± 1.46	76.33 ± 1.29
National Catheter (n = 3)	15	82.93 ± 1.28	75.13 ± 1.06
Rusch (n = 1)	5	82.00 ± 1.00	75.00 ± 0.71
Rusch (n = 1)	5	76.40 ± 0.89	71.40 ± 1.52
Rusch (n = 1)	5	82.80 ± 0.45	73.40 ± 1.14

smallest diameter (14.5 mm) and resting volume (0.15 ml). Franklin's softway cuff was the thickest PVC cuff (.268 mm), had a relatively small diameter (17.9 mm), and contained a low resting volume (4.0 ml). The National Catheter "intermediate hi-lo" cuff was thicker (.059 mm), shorter (33.5 mm), slightly smaller in diameter (28.4 mm), and contained approximately half the resting volume (9.9 ml) as compared with the regular "hi-lo" cuff. Concept's "C-Flex" cuff was short (32.1 mm), narrow (16.6 mm), and had a low resting volume (2.4 ml).

Discussion

These data show a rather wide degree of variation in the physical and behavioral characteristics of tubes and cuffs from different manufacturers and even some dimensional variability in tubes from the same manufacturer. Variations in force to collapse a tube, angle to kink a tube, bevel-to-cuff distance, tube wall thickness, and internal diameter are important clinically, whereas variability in bevel characteristics and tube curvature radius are less important to proper function and use. Dimensional variations in tubes from the same manufacturer may indicate need for additional manufacturing and quality controls. The large curvature radius of the Rusch RR tube (15.78 cm) may explain the clinical impression that this tracheal tube is easier to pass through the vocal cords transnasally than other tubes with smaller radii. But, its blunt tip (56°) may be more traumatic in the nose than the National Catheter tube with its tip beveled to 39°. Tube tip softness and geometry are probably more important than bevel angle in vocal cord and tracheal mucosal trauma, but they have little effect on function. A large deviation of bevel direction from 90° left as seen on Portex, Lanz, and Rusch safety tubes (17° above or below 90°), is also probably not a major factor in tube-related tip trauma to the nose, larynx, and trachea.

If the bevel direction were changed from left to right there would theoretically be less chance of distal lumen obstruction against the medial wall of the right bronchus or right upper lobe bronchus occlusion if the right main stem bronchus is inadvertently intubated. Distance from cuff to tube tip determines how far above carina the distal end of the tube lies when the proximal end of the cuff is correctly placed approximately 2 cm below the vocal cords to allow for changes in tube position with head flexion and extension (13). This tip-to-cuff distance would be decreased if the Murphy Eye were omitted. Too short a distance from distal end of cuff to bevel can predispose a large diameter "floppy" cuff to herniate over the bevel lumen if the cuff is overinflated or when nitrous oxide increases the volume of a properly inflated cuff (2).

The 1974 American National Standards Institute (ANSI) standard for cuffed orotracheal and nasotracheal tubes states that size 8 tracheal tubes must have a circular not oval cross section as measured in Franklin's softway tube (A-P = 8.76 and lateral-lateral 7.5 mm). A small degree of elliptical shape (Portex) may be due to compression during storage. A tube with a wide lateral elliptical section may put excessive lateral pressure on vocal cords. Large differences between tube wall thickness and thinness (Rusch RR Δ = 0.74 mm, Bivona Silastic Δ = .36 mm, and Rusch safety Δ = .33 mm) may indicate a need for the manufacturer to alter extrusion techniques and quality controls. The thinness of the Lanz tube (1.15 mm) may account for its low force to collapse (1126 and 1020 g) and tendency to kink (84 and 94°). Other characteristics such as lumina in the tube wall (cuff inflating line), tube geometry (ridges), and indentation hardness (durometer reading) must also be factors in ease of collapse and kinking. The Silastic Bivona tube's longitudinal ridges (approximately 40) and relative wall thickness (1.79 to 2.15 mm) probably account for the large initial force (2803 g) for collapse and its resistance to kink (60°). The hard, thick-walled, rubber Rusch tube's ability to resist collapse (3103 g) is probably due to the nature of the rubber. This may also explain why it kinked easier (87°) than polyvinylchloride (PVC) and Silastic tubes. Franklin's resistance to collapse was low (1047 and 1032 g) even though its anterior-posterior diameter measured more than its lateral-lateral dimension (Δ = 1.26 mm). Also, the slight increase in the Lanz tube's anterior-posterior

dimension (8.37 mm) over its lateral-lateral measurement (8.11 mm) did not increase its force to collapse (1126 g) close to the National Catheter tube (1897 g).

Indentation hardness (durometry) of Silastic and rubber tracheal tubes could not be measured with the Shore type A-2 durometer hardness meter. As expected, hardness decreased as thermolabile PVC tubes warmed to body temperature (Table 4). Our finding that one group of Portex tubes was 10 units less hard that the other Portex tubes studied is explained by the fact that this group, according to the company, was produced for nasal rather than oral use. The Portex Company reduced hardness during formulation of the plastic material, presumably in an effort to reduce nasal mucosal trauma. Soft tubes like the Portex nasal tube (hardness 65.4) may be less traumatic but they may conceivably collapse more easily. Variability in hardness seen with Rusch PVC tracheal tubes suggests the need for an indentation hardness standard (75 ± 2 at 37 C for PVC) and/or publication of material hardness by the manufacturer. Reluctance to collapse and kink increases safety but failure to conform easily to a patient's anatomy may be hazardous. How to measure and equate in vitro tube behavior with in vivo safety and function is still not well understood even though it should be an important purchasing consideration.

Variability in physical characteristics between cuffs is reflected clinically in intracuff pressure at seal and degree and area of tracheal mucosal trauma. Long cuffs like the Shiley cuff (45 mm) have greater contact with tracheal mucosa than small diameter short cuffs (Rusch RR) and therefore may traumatize more mucosal surface. Another factor in cuff-related trauma is the amount of cuff movement with head motion (12). A tracheal tube may move within a large diameter floppy cuff with head flexion and extension thereby minimizing cuff movement. On the other hand, a short, small diameter cuff (latex cuff on Rusch RR tube) moves with the tube when head flexion and extension occurs, thereby abraiding tracheal mucosa. Both Portex "profile cuff" and National Catheter "intermediate hi-lo" cuff have less lateral surface length (35.1 and 33.5 mm, respectively) than the regular hi-lo cuff (43.3 mm) to contact tracheal mucosa and should therefore traumatize less mucosa. They differ slightly in design, thickness, and diameter but have the same resting volume (9.9 ml).

Mackenzie reports the average adult tracheal breath holding diameter to be 24.3 mm in males and 20.5 mm in females (14). If a cuff is to seal at a low intracuff pressure, cuff diameter must equal or exceed tracheal diameter. Cuffs on the Rusch RR, Franklin, Shiley, and Concept tubes do not exceed average adult male tracheal diameter and therefore should not be classified as "low pressure cuffs" unless intracuff pressure is controlled at a low pressure. Cuffs with larger diameters and resting volumes can be classified as low pressure cuffs because they have the ability to provide tracheal seal at low intracuff pressures.

Thick-walled, large diameter cuffs form large lateral folds with inflation in vivo thereby allowing liquids to channel through folds down the trachea (15). Bivona's Silastic "aire-cuff" will form large folds at low intracuff pressures thereby allowing tracheal aspiration because its cuff has a larger diameter (31.7 mm) and is thick (.213 mm). Franklin's cuff is also thick (.268 mm) but its diameter is small (17.9 mm) so that at seal in an adult trachea (diameter 20 to 24 mm) the cuff will be stretched thereby preventing formation of folds and possible aspiration.

The Bureau of Medical Devices of the Federal Drug Administration has recently designed a new test protocol to determine force necessary to bring tracheal tubes into anatomic position (4). This force is exerted posteriorly against the larynx and should be minimized if possible. Force to deform a tube to conform to airway anatomy is theoretically influenced by tube hardness, thickness, size, geometry, and temperature. Presumably anatomically shaped tubes should undergo less deformation in the larynx if properly placed and be less traumatic to the airway, but the axial longitudinal force and stiffness to keep them in place must be large enough to prevent dislocation upwards (16).

We measured collapse force and kink angle twice 30 seconds apart to check material memory. The Portex "blue line" tube's tendency to collapse easier the second time (Δ = 212) as compared with other tracheal tubes (Table 3) may make molding easier and may account for the rather wide difference between its anterior-posterior and lateral-lateral internal diameters (Table 2). The Bivona tube has the most memory on the kink test (kinked easier the second time (Δ = 18), but not so on the collapse test (Δ = 37). This may be due to its longitudinal ridges and/or the properties of silastic. The Rusch "safety" tube's resistance to kinking (52°) may be explained because its maximum thickness (1.60 mm) exceeds that of other PVC tubes.

Recent data (1) from the University of Utah Research Institute substantiates ulceration over the arytenoid cartilages in all dogs intubated for 32 hours with thermolabile PVC tubes. Checking such tube-

inflicted trauma against relevant tracheal tube physical and behavioral characteristics may help define the "ideal" tracheal tube: a soft, thermolabile tracheal tube that resists kinking and collapse. Argyle, National Catheter, Ohio, Portex, Rusch "safety," and Shiley thermolabile PVC tracheal tubes resisted collapse and kinking better than Lanz and Franklin "softway" tubes. Knowledge of cuff physical characteristics and current recommendations for use (2, 15, 17) is also necessary to choose an appropriate cuff. The ideal cuff should be thin walled, soft, tough, compliant, and moderately long. It should have a moderately large resting volume and diameter larger than tracheal diameter. Argyle, Lanz, National Catheter "hi-lo" and "intermediate hi-lo," Ohio, and Portex "profile" cuffs were thinner and had larger diameters than Rusch latex (RR tube), Rusch "super safety," Franklin "softway," and Concept "C-Flex" cuffs. Shiley's cuff was thin but its diameter was less than the average male tracheal diameter. Bivona's cuff had a large diameter but its cuff was 7 times thicker than National Catheter's "hi-lo" cuff. Proper choice of a cuffed tracheal tube that approximates the ideal should help increase intubation safety and allow prolonged use of translaryngeal tracheal airways.

REFERENCES

1. Yates WG, Shaap RN, McGill LD. An evaluation of tracheal damage test method for cuffed tracheal tubes. Salt Lake City, UT: University of Utah Research Institute, October 1979.
2. Bernhard WN, Yost LC, Turndorf H, et al. Physical characteristics of and rates of nitrous oxide diffusion into tracheal tube cuffs. Anesthesiology 1978;48:413–17.
3. Lindholm CE, Carroll RG. Evaluation of tube deformation pressure in vitro. Crit Care Med 1975;3:196–9.
4. Brdlik GE, Foster LA. Test protocol two for orotracheal, nasotracheal, and tracheostomy tubes for prolonged use. Technical Report, Division of General Medical Device Standards, Bureau of Medical Devices, Federal Drug Administration, Silver Spring, MD August 1980.
5. Kambic V, Radsel Z. Intubation lesions of the larynx. Br J Anaesth 1978;50:587–90.
6. Battersby EF, Hatch DJ, Towey RM. The effects of prolonged nasotracheal intubation in children. Anaesthesia 1977;32:154–7.
7. Deane RS, Shinozaki T, Morgan JG. An evaluation of cuff characteristics and incidence of laryngeal complications using a new nasotracheal tube in prolonged intubations. J Trauma 1977;17:311–4.
8. Lewis FR, Blaisdell FM, Schlobohm RM. Incidence and outcome of posttraumatic respiratory failure. Arch Surg 1977;112: 432–43.
9. Lewis FR, Schlobohm RM, Thomas AN. Prevention of complications from prolonged tracheal intubation. Am J Surg 1978; 135:452–7.
10. Gregory GA. Respiratory care of the child. Crit Care Med 1980; 8:582–7.
11. Stauffer JL, Olsen DE, Petty TL. Complications and consequences of endotracheal intubation and tracheotomy. Am J Med 1981;70:65–76.
12. American Society for Testing and Materials. Annual book of ASTM standards. Philadelphia: American Society for Testing and Materials, 1974;37:516–9.
13. Conrardy PA, Goodman IR, Lainge F, Singer MM. Flexion and extension of the neck. Significant alteration of endotracheal tube position. Crit Care Med 1979;4:8–12.
14. MacKenzie CF, Shin B, Whittey N, Helrich M. Human tracheal circumference as an indicator of correct cuff size. Anesthesiology 1980;53:S414.
15. Bernhard WN, Cottrell JE, Sivakumaran C, Patel K, Yost L, Turndorf H. Adjustment of intracuff pressure to prevent aspiration. Anesthesiology 1979;50:363–6.
16. Ripoll I, Lindholm CE, Carroll R, Grenvik A. Spontaneous dislocation of endotracheal tubes. Anesthesiology 1978;49:50–2.
17. Nordin U. The trachea and cuff induced tracheal injury. Acta Otolaryngol 1977;Suppl 345.

ANESTH ANALG
1982;61:42-5

Cardiovascular Depression during Halothane Anesthesia in Infants: A Study of Three Induction Techniques

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FRIESEN, R. H., LICHTOR, J. L.: Cardiovascular depression during halothane anesthesia in infants: a study of three induction techniques. Anesth Analg 1982;61:42-5.

Hemodynamic changes during three techniques for induction of halothane anesthesia were studied in 90 healthy infants aged 5 to 26 weeks who were randomly divided into three groups of 30 patients each. In group I, anesthesia was induced using halothane in concentrations that were increased to 3%. In group II, atropine, 0.02 mg/kg, was given intramuscularly before induction, followed by induction as in group I. In group III, halothane in concentrations that were increased to 1.25% was followed by intramuscular succinylcholine, 2 mg/kg, 90 seconds after the start of induction. In all three groups N_2O 3 L/min and O_2 2 L/min were employed using a non-rebreathing system. Heart rate (HR) and blood pressure (BP) were recorded at 1-minute intervals for 20 minutes. HR decreased 30% in group I, 18% in group II ($p < 0.01$), and 29% in group III. BP decreased 50% in group I ($p < 0.01$), 34% in group II, and 33% in group III. During halothane induction in infants, bradycardia can be minimized with preoperative atropine; the degree of hypotension can be diminished with either preoperative atropine or the use of intramuscular succinylcholine combined with lower concentrations of halothane.

Key Words: ANESTHESIA: pediatric; ANESTHETICS, Volatile: halothane; AGE FACTORS: halothane.

HALOTHANE continues to be the most commonly utilized anesthetic agent for pediatric patients. The cardiovascular depressant effects of this drug are generally known, and studies have documented these effects in children (1-3). Although a systematic study of the effects of halothane on systolic blood pressure (BP), mean arterial pressure (MAP), and heart rate (HR) of infants less than 6 months of age has not been performed, it is widely believed that cardiovascular depression is more pronounced in infants than in older children and adults. Thus, concomitant use of other drugs, notably atropine and succinylcholine, has been suggested to minimize the hemodynamic changes seen in infants during halothane administration (4).

This prospective study was undertaken to document changes in HR, BP, and MAP in infants less than 6 months of age during three techniques of anesthetic induction utilizing halothane.

Methods

Ninety infants aged 5 to 26 weeks scheduled for elective surgical procedures were studied. All were of A.S.A. physical status I or II and were without known cardiac or pulmonary disease. They were randomly divided into three groups of 30 patients each.

Patients in group I were not premedicated and anesthesia was induced using halothane in gradually increasing concentrations up to 3% in N_2O 3 L/min and O_2 2 L/min via a non-rebreathing system (Jackson Rees modification of Ayre's T-piece). Orotracheal intubation was performed during deep halothane anesthesia after which the halothane concentration was reduced to 1.0%.

Patients in group II were premedicated with atropine, 0.02 mg/kg, intramuscularly 20 to 60 (mean 39 ± 14 SD) minutes before induction, followed by induction and intubation as in group I.

Patients in group III were not premedicated and anesthesia was induced using halothane in gradually increasing concentrations up to 1.25% in N_2O 3 L/

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min and O_2 2 L/min. Succinylcholine, 2 mg/kg, was administered intramuscularly 90 seconds after the start of induction. Orotracheal intubation was performed under light halothane anesthesia with muscle relaxation. Halothane concentration was kept at 1.25% following intubation.

All anesthetic inductions were carried out by resident physicians with one of the authors (R.H.F.) in attendance. Early in the induction a peripheral intravenous catheter was inserted and 5% dextrose in Ringer's lactate solution, 8 ml/kg, was infused during the 20-minute study period.

Utilizing a Dinamap 847 monitor and 950 recorder (Critikon, Tampa, FL), HR, BP, and MAP were recorded at 1-minute intervals for 20 minutes beginning just before induction and ending before surgical stimulation. Statistical significance of data was evaluated using one-way analysis of variance.

Results

There were no significant differences among the groups with respect to age, weight, hematocrit level, fasting time, and physical status (Table 1).

Each patient's lowest HR, BP, and MAP was used to determine the group's mean lowest HR, BP, and MAP. These mean lowest values are shown in Table 2 along with preinduction values and percentage change. Patients in group I had a 30% decrease in HR. This decrease was significantly ($p < 0.01$) reduced to 18% by premedication with atropine (group II) but was not significantly different from the decrease in HR observed in patients given light halothane anesthesia plus intramuscular succinylcholine (group III).

BP decreased 50% from preinduction levels in group I, whereas in groups II and III, BP decreased 34% and 33%, respectively. Similarly, MAP decreased 54% in group I, 44% in group II, and 40% in group III. The mean lowest BP and MAP values were significantly ($p < 0.01$) lower in group I than in the other two groups.

TABLE 1

Infant Population*

	Group I	Group II	Group III
Age (wk)	14.0 ± 6.7	12.7 ± 7.0	12.8 ± 6.1
Weight (kg)	5.7 ± 1.5	5.5 ± 1.3	5.3 ± 1.4
Hematocrit (%)	36.4 ± 3.3	36.1 ± 4.1	33.5 ± 4.1
Fasting times (hr)	6.3 ± 2.1	6.2 ± 1.7	7.0 ± 1.8

* Values are means ± SD; n = 30 in each group.

TABLE 2

Changes in Heart Rate (HR), Systolic Blood Pressure (BP), and Mean Arterial Pressure (MAP) during Three Anesthetic Induction Techniques in Infants*

	Group I	Group II	Group III
Preinduction HR	163 ± 26	198 ± 18†	163 ± 21
Lowest HR	114 ± 17	162 ± 14†	116 ± 23
% change	−30 ± 16	−18 ± 8†	−29 ± 15
Preinduction systolic BP	100 ± 15	98 ± 14	103 ± 13
Lowest systolic BP	50 ± 13†	65 ± 14	69 ± 13
% change	−50 ± 15†	−34 ± 15	−33 ± 14
Preinduction MAP	84 ± 15	85 ± 14	84 ± 13
Lowest MAP	39 ± 8†	48 ± 11	50 ± 10
% change	−54 ± 8†	−44 ± 10	−40 ± 11

* Values are means ± SD; n = 30 in each group.
† Significantly different ($p < 0.01$) from the other groups.

Discussion

Pediatric anesthesiologists have felt for some time that young infants are more susceptible to the cardiovascular depressant effects of halothane than are older children and adults. Although the support for this concept has been mostly anecdotal, there is some supportive evidence in the literature. At equipotent (ED_{50}) doses of halothane following atropine premedication, Nicodemus et al (2) observed hypotension in 17% of infants less than 6 months of age, in 8% of those aged 6 to 24 months, and in none of those aged 25 to 48 months. A similar age-related trend has also been reported in young rats by Cook et al (5). In a retrospective study of normal infants less than 24 weeks of age undergoing halothane and nitrous oxide anesthesia from induction to intubation, Diaz and Lockhart (6) reported a 49% incidence of hypotension (30% or greater decrease in systolic BP) and a 9% incidence of bradycardia (HR less than 80 beats/min).

The mechanism for this apparent sensitivity to halothane has yet to be elucidated, although several age-related predisposing factors have been suggested. These include greater anesthetic requirement (2, 5), anemia (7), diminished baroreceptor response (8), greater alveolar uptake of inhalation anesthetics (9), excessive fasting times (6), and history of prematurity (6, 7).

The present study confirms that anesthetic induction with halothane and nitrous oxide is associated with significant hypotension in the infant from 5 to 26 weeks of age. The mean of the lowest blood pressures in patients in group I showed a decrease in

systolic BP of 50% and in MAP of 54% (Table 2). We do not feel that the hypotension was exaggerated by falsely elevated preinduction BP values. Although these values were obtained just before induction in agitated infants, the mean preinduction systolic BP of 100 mm Hg was only slightly higher than the observed mean normal systolic BP of 96 mm Hg in infants 6 weeks and 6 months of age (10).

The decrease in HR in group I was also statistically significant, the mean lowest HR obtained being 114 beats per minute, or 30% less than before induction (Table 2). Seven patients in this group had heart rates that decreased to less than 100 beats per minute. Decreases in HR are clinically important in the infant, as the infant's low ventricular compliance makes cardiac output highly dependent on HR (11).

Reversal of halothane-associated cardiovascular depression by atropine has been observed in older children (3, 12) and has often been recommended for management of infants (4, 13). Barash et al (3) studied atropine administration during halothane anesthesia in children 19 months to 12 years of age and observed that HR, BP, and cardiac output all improved significantly.

This study indicates that premedication with atropine, 0.02 mg/kg, offers a measure of protection against the cardiovascular depression during induction of anesthesia in infants with halothane and nitrous oxide. Prevention of bradycardia was achieved in group II (Table 2). Although the decrease in BP was not completely prevented by atropine, the mean lowest levels of systolic BP and MAP were significantly higher than in group I (Table 2). This protective effect was observed throughout the induction period.

The combination of lower dose halothane induction with muscle relaxation by intramuscular succinylcholine also protected against severe decreases in systolic BP and MAP (Table 2). Systolic BP in group III was similar to that observed in infants given atropine and was significantly higher than the systolic BP of infants in group I (Table 2). These results support Smith's long-standing recommendation (4, 14) that intramuscular succinylcholine be used to avoid the hypotension associated with halothane induction in infants.

The decrease in HR in patients in group III was similar to that observed in group I (Table 2). This similarity occurred in spite of the lower dose of halothane and the maintenance of BP in group III. Although bradycardia is less frequent following intramuscular succinylcholine than following intravenous administration (4), six infants in group III developed heart rates less than 100 beats per minute which were temporally related to intramuscular succinylcholine. Atropine should prevent this.

TABLE 3
Timing of Events during Three Anesthetic Induction Techniques in Infants*

	Group I	Group II	Group III
		min	
Intubation	6.5 ± 1.5	6.9 ± 1.4	4.2 ± 0.8
Lowest HR	8.5 ± 4.6	11.3 ± 5.4	7.6 ± 4.1
Lowest BP	9.9 ± 5.0	11.3 ± 5.5	14.2 ± 5.3
Lowest MAP	10.4 ± 5.0	10.4 ± 5.2	13.3 ± 5.1

* Values are means ± SD minutes into induction; n = 30 in each group.

The timing of certain events during these induction techniques is shown in Table 3. The lowest levels of BP and HR were usually observed 2 to 4 minutes after intubation in groups I and II, recalling the finding of Salem et al (7) that cardiac arrest in infants receiving halothane anesthesia for herniorrhaphy most commonly occurred a few minutes after intubation. This suggests that the period of greatest risk during halothane induction in infants is not the time of greatest inspired halothane concentration (intubation in groups I and II), but rather the "quiet period" between intubation and incision when the level of stimulation is low, but the arterial level of halothane may still be high.

With regard to the monitoring device used in this study, the Dinamap 847 (Critikon) was found to be of acceptable accuracy in both neonates and infants less than 26 weeks of age (15, 16).

Our conclusions regarding halothane anesthetic induction in infants 5 to 26 weeks of age are that (*a*) premedication with intramuscular atropine, 0.02 mg/kg, significantly reduces the decrease in HR, BP, and MAP; and (*b*) use of intramuscular succinylcholine with lower halothane doses significantly reduces the decrease in BP and MAP.

In applying these conclusions to clinical practice, we have several general recommendations. Halothane remains, for a variety of reasons, the anesthetic of choice for most procedures on infants. Although no apparent morbidity was associated with the hypotension observed in group I patients, it seems safer to utilize the protection afforded by premedication with atropine. We do not routinely use succinylcholine in infants, as we are generally satisfied with atropine's protection against cardiovascular depression. However, in management of particularly high risk infants, such as those with bronchopulmonary dysplasia or history of prematurity, we suggest that the protective effects of both atropine premedication and induction

with low concentration halothane aided by intramuscular succinylcholine would be advantageous.

REFERENCES

1. McGregor M, Davenport HT, Jegier W, Sekelj P, Gibbons JE, Demers PP. The cardiovascular effects of halothane in normal children. Br J Anaesth 1958;30:398–408.
2. Nicodemus HF, Nassiri-Rahimi C, Bachman L, Smith TC. Median effective doses (ED50) of halothane in adults and children. Anesthesiology 1969;31:344–8.
3. Barash PG, Glanz S, Katz JD, Taunt K, Talner NS. Ventricular function in children during halothane anesthesia: an echocardiographic evaluation. Anesthesiology 1978;49:79–85.
4. Smith RM, Anesthesia for infants and children. 4th ed. St Louis: CV Mosby, 1980:118, 256.
5. Cook DR, Brandom BW, Shiu G, Wolfson B. The inspired median effective dose, brain concentration at anesthesia, and cardiovascular index for halothane in young rats. Anesth Analg 1981;60:182–5.
6. Diaz JH, Lockhart CH. Is halothane really safe in infancy? Anesthesiology 1979;51:S313.
7. Salem MR, Bennett EJ, Schweiss JF, Baraka A, Dalal FY, Collins VJ. Cardiac arrest related to anesthesia: contributing factors in infants and children. JAMA 1975;233:238–41.
8. Ware R, Robinson S, Gregory GA. Effect of halothane on baroreceptor response in newborn and adult rabbits. Anesthesiology 1979;51:S325.
9. Salanitre E, Rackow H. The pulmonary exchange of nitrous oxide and halothane in infants and children. Anesthesiology 1969;30:388–94.
10. de Swiet M, Fayers P, Shinebourne EA. Systolic blood pressure in a population of infants in the first year of life: the Brompton study. Pediatrics 1980;65:1028–35.
11. Friedman WF. The intrinsic physiologic properties of the developing heart. Prog Cardiovasc Dis 1972;15:87–111.
12. Sagarminaga J, Wynands JE. Atropine and the electrical activity of the heart during induction of anaesthesia in children. Can Anaesth Soc J 1963;10:328–41.
13. Rackow H, Salanitre E. Modern concepts in pediatric anesthesiology. Anesthesiology 1969;30:208–33.
14. Smith RM. Pediatric anesthesia in perspective. Anesth Analg 1978;57:634–46.
15. Kimble KJ, Darnall RA Jr, Yelderman M, Ariagno RL, Ream AK. An automated oscillometric technique for estimating mean arterial pressure in critically ill newborns. Anesthesiology 1981;54:423–5.
16. Friesen RH, Lichtor JL, Indirect measurement of blood pressure in neonates and infants utilizing an automatic noninvasive oscillometric monitor. Anesth Analg 1981;60:742–5.

Nitrous Oxide-Oxygen Sedation for Minor Surgery

Nitrous oxide-oxygen sedation has been used safely in a pediatric office for approximately 3000 uncomfortable procedures such as laceration repairs in children and teenagers. The youngest patients treated were 16 months old; the oldest were young adults. Nitrous oxide-oxygen mixtures were administered using a nasal inhaler. Nitrous oxide concentrations used ranged from 50% to 67%. While sedated nine patients vomited without evidence of pulmonary aspiration of gastric contents. No provisions were made for scavenging the nitrous oxide. Ambient nitrous oxide levels were not reported. There was a decrease in levels of fear and apprehension, resulting in happier children, parents, and medical personnel. *(Griffin GC, Campbell VD, Jones R: Nitrous oxide-oxygen sedation for minor surgery: experience in a pediatric setting. JAMA 1981;245:2411–3)*
(See also—Robertson WO: Editorial: Managing pain in children. JAMA 1981;245:2429–30)

ANESTH ANALG
1982;61:46-8

Treatment of Bladder Pain with Transsacral Nerve Block

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SIMON, D. L., CARRON, H., AND ROWLINGSON, J. C.: Treatment of bladder pain with transsacral nerve block. Anesth Analg 1982;61:46-8.

Fifteen patients with bladder spasticity and pain of three different etiologies were referred to the pain clinic by urologic specialists. These patients were refractory to all prior methods of treatment, excluding major surgical procedures. In a prospective study started in 1976, these patients were treated with transsacral nerve blocks using 0.25% bupivacaine and, in most cases, subsequent 6% aqueous phenol at the right S-3 ventral foramen. If indicated, transsacral nerve blocks were performed at other levels, as described in the text. Of the patients studied 53% have had significant or complete relief of pain for an average of 26.5 months. The associated morbidity was negligible and there was no mortality. This is in contrast to the morbidity and mortality associated with some major surgical "curative" procedures. The technique is proposed as a successful and economical approach to treatment that can be managed on an outpatient basis.

Key Words: PAIN: bladder; ANESTHETIC TECHNIQUES, Regional: transsacral.

ONE OF THE most difficult treatment problems confronting the pain clinic specialist, consultant anesthesiologist, neurosurgeon, and urologist alike is the painful contracted bladder. Radiation, chronic infection, calculi, interstitial cystitis, spinal cord injury or disease, tuberculosis, and virtually any inflammatory lesion of the bladder can cause urgency, frequency, and pain on urination associated with a reduction in bladder capacity and incontinence. Many patients become "bladder cripples" because the frequency of voiding makes it impossible to pursue normal activities. The concomitant chronic pain may result in overwhelming psychosocial changes.

Treatment of bladder spasticity in the past has been based primarily on pharmacologic and surgical management following diagnostic studies. The results of pharmacologic treatment are often unsatisfactory. Following surgical denervation, including selective rhizotomy, approximately 50% of patients report partial or complete relief of pain and other symptoms (1). Success rates of up to 65% are reported with extensive palliative or "curative" surgical procedures. The mortality rate reported with enterocystoplasty, however, varies from 2.7% to 8.7%, with poor results in 35% of patients in one series (2, 3) and urinary or fecal fistulas in up to 25% (2).

The management of interstitial cystitis has received extensive attention in the literature as well. The lack of uniform success with any particular treatment has resulted in a multitude of therapeutic approaches. Surgical procedures performed include cystolysis (4), bladder augmentation (3), and, usually as a last resort, creation of an ileal loop (urinary diversion). Hydraulic bladder distention, intravesical silver nitrate, dimethylsulfoxide, and immunosuppressive agents have been tried. Most treatments have met with limited success.

Management of bladder dysfunction with local anesthetic transsacral nerve blocks has been utilized in the past for diagnostic and prognostic purposes. We have found no prospective studies with long-term follow-up that have evaluated the efficacy of local anesthetic or neurolytic transsacral blocks alone. In view of the high morbidity and mortality reported for some surgical procedures performed for treatment of bladder spasticity, we were interested in evaluating the success of treatment with transsacral nerve blocks.

Methods

A prospective evaluation of the efficacy of transsacral nerve block in treatment of bladder pain, fre-

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Received from the Department of Anesthesiology, University of Virginia Medical Center, Charlottesville, Virginia 22908. Accepted for publication September 10, 1981.
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quency, and urgency associated with a painful, contracted, or spastic bladder was undertaken. Fifteen patients between the ages of 24 and 60 years were studied from 1976 to 1981. All patients were referred to our pain clinic by urologic specialists, usually after cystometric and other diagnostic studies were completed and oral (including anticholinergic), parenteral, or intravesical pharmacologic management failed.

Following patient evaluation, informed verbal consent was obtained. The protocol was approved by the Human Investigation Committee and written consent was not deemed necessary because transsacral nerve block is an accepted therapeutic procedure. All patients underwent an initial right S-3 transsacral block with 2 ml of 0.25% bupivacaine using Moore's technique (5). That is, the patients were placed in the prone position and the appropriate landmarks identified. Through a skin wheal, a 22-gauge spinal needle was introduced perpendicular to the skin until bone was contacted. Then, entry into the foramen was sought and the needle advanced to the ventral foramen. Intermittent aspiration for blood and/or cerebrospinal fluid was performed. If there was no subjective improvement over the ensuing 24 to 48 hours, the injection was repeated at the left S-3 foramen. Within another 24- to 48-hour evaluation period, additional transsacral blocks were performed at other levels (S-4 in one patient, S-2 in seven patients) in patients who failed to respond or who had only partial symptomatic improvement. Of the 15 patients studied, 12 patients had significant symptomatic relief following nerve block with bupivacaine. Of these 12 patients 10 consented to neurolytic block with 2 ml of 6% aqueous phenol injected at the level that produced improvement in symptoms. No patient received more than one neurolytic block at each visit or a total of three such blocks. Statistical analysis could not be performed because randomization criteria for valid statistical testing was not incorporated and the size of the patient population was limited.

Results

The results of the study are summarized in the Table. Of the 10 patients who had 6% aqueous phenol nerve blocks following successful local anesthetic block, seven reported significant long-lasting pain relief at follow-up, one reported 1 week of analgesia, and two received no benefit from the procedure. Five patients had nerve blocks with bupivacaine only. One of these patients obtained significant and persistent relief of pain and refused planned neurolytic block.

TABLE

Patient Data on Diagnosis, Agent(s) Used for Transsacral Nerve Block, and Results of Treatment*

Patient no.	Diagnosis	Agent(s) used for nerve block	Duration of pain relief
1	IC	Bupivacaine; 6% phenol	P
2	IC	Bupivacaine	T
3	IC	Bupivacaine	N
4	IC	Bupivacaine; 6% phenol	P
5	IC	Bupivacaine; 6% phenol	P
6	IC	Bupivacaine; 6% phenol	P
7	IC	Bupivacaine	N
8	IC	Bupivacaine; 6% phenol	N
9	IC	Bupivacaine; 6% phenol	N
10	IC	Bupivacaine; 6% phenol	P
11	IC	Bupivacaine	T
12	PIC	Bupivacaine	P
13	PIC	Bupivacaine; 6% phenol	P
14	PIC	Bupivacaine; 6% phenol	T
15	NB	6% phenol	P

* Abbreviations used are: IC, interstitial cystitis; PIC, postirradiation cystitis; NB, neurogenic bladder; P, significant and persistent; T, temporary (less than 8 weeks); N, none.

Two patients did not maintain contact with the clinic and moved their residences to other areas. On follow-up, it was found that these two patients had significant temporary pain and other symptomatic relief (average of 4.5 weeks duration). The other two patients had no symptomatic improvement following bupivacaine blocks, and thus were not considered candidates for phenol injection. The patients who experienced significant pain relief generally also noted dramatic improvement in other pathologic bladder symptoms, including frequency and urgency. Those patients who were treatment failures remained bladder cripples with further therapy, including surgical intervention, not offered during the period of follow-up.

Of this study group, five of the 11 patients with interstitial cystitis had complete or significant sustained pain relief; two had only temporary symptomatic relief, and four had no benefit. Of three patients with postirradiation hemorrhagic cystitis, two obtained persistent pain relief, whereas the third patient had only temporary symptomatic improvement. The one patient with a neurogenic spastic bladder reported no recurrence of pain after 22 months.

The average follow-up period was 24 months, and the average duration of response in the patients with persistent pain relief was 26.5 months. Complications associated with transsacral block in this study were minimal and transient. One patient experienced hypesthesia of the right side of the anus for 1 day following bupivacaine block of the S-3 nerve. Early in the series, a patient noted hypesthesia of the S-1

dermatome for 2 weeks following S-2 block with bupivacaine. No patients suffered urinary or rectal incontinence or other major complications such as toxic reaction to the drugs injected, local infection or hematoma, broken needles, impotence, or subarachnoid injection.

Discussion

The bladder is under voluntary and involuntary, or reflex neurogenic, control and is regulated by cholinergic and adrenergic innervation. Therapeutic denervation is accomplished by interruption of one or more of the sacral nerves S-2, S-3, and S-4, which contain parasympathetic fibers to the detrusor muscle and somatic fibers to the pelvic floor (6, 7). The rationale for first attempting sacral nerve blocks is based on evidence documenting dominance of the S-3 and S-4 nerve roots in detrusor muscle contraction (8–10). Multiple attempts at denervation may occasionally be required because of the overlapping nervous innervation which is variable among patients. Not uncommonly, there is a unilateral predominance in the innervation of the detrusor reflex activity (10). Ablation of the ventral root output may be necessary for relief of bladder symptoms, especially with a spastic bladder (11). The ultimate goals of transsacral block should include restoration of normal bladder activity and provision of symptomatic relief without affecting normal detrusor contraction or sensation, erection, or production of urinary or rectal incontinence. Atony of the bladder rarely occurs as a complication of selective unilateral neurolytic block or selective rhizotomy because of its multiple and bilateral nerve root innervation.

Phenol has been used as a neurolytic agent since the mid-1920s (12). In 1% to 2% concentrations, phenol has been used as a topical anesthetic. Concentrations greater than 5% result in protein coagulation and tissue destruction (13). Compared to alcohol, phenol has more rapid onset of action, is less of a tissue irritant, and is less likely to result in neuritis (13).

Results of treatment in this group of patients with transsacral blocks were equal or superior to those of other studies reported using other forms of treatment. The patients in this study served as their own control group, as these patients were previously refractory to other forms of medical and surgical therapy, both invasive and noninvasive. Of the patients studied, 53% achieved significant pain relief following a nonsurgical procedure with minimal morbidity and no mortality. Although the morbidity and mortality following rhizotomy may also be minimal, the success rate of selective fascicle rhizotomy is disappointing. Other forms of treatment, medical or surgical, may be associated with a significant morbidity or mortality. The block procedures can be performed safely and accurately on an outpatient basis and at minimal cost and time expenditure to the patient and anesthesiologist. Brief follow-up observation is required for detection of side effects or complications.

REFERENCES

1. Torrens M, Hald T. Bladder denervation procedures. In: Turner-Warwick R, Graham WC, eds. Urologic clinics of North America. Philadelphia: WB Saunders, 1979:283–93.
2. Kuss R, Bitker M, Camey M, Chatelain C, Lassau J. Indications and early and late results of intestinocystoplasty: a review of 185 cases. J Urol 1970;103:53–63.
3. Smith RB, VanCangh P, Skinner DG, Kaufman JJ, Goodwin WE. Augmentation enterocystoplasty: a critical review. J Urol 1977;118:35–9.
4. Worth PHL, Turner-Warwick RT. The treatment of interstitial cystitis by cystolysis with observations on cystoplasty. Br J Urol 1973;45:64–71.
5. Moore DC, Regional block. Springfield, IL: Charles C Thomas, 1979:473–80.
6. Torrens MJ. The effect of selective sacral nerve blocks on vesical and urethral function. J Urol 1974;112:204–5.
7. Westgate HD. Selective percutaneous sacral root blockade with phenol in neurovesical dysfunction. Can Anaesth Soc J 1970;17: 456–63.
8. Mierowsky AM. The management of chronic interstitial cystitis by differential sacral neurectomy. J Neurosurg 1969;30:604–7.
9. Rockswold GL, Chou SN, Bradley WE. Reevaluation of differential sacral rhizotomy for neurogenic bladder disease. J Neurosurg 1978;48:773–8.
10. Rockswold GL, Bradley WE, Chou SN. Differential sacral rhizotomy in the treatment of neurogenic bladder dysfunction. J Neurosurg 1973;38:748–54.
11. Nagib A, Leal J, Varis HC. Successful control of selective sacral rhizotomy for treatment of spastic bladder and ureteric reflex in paraplegics. Med Serv J Can 1966;22:576–81.
12. Wood KM. The use of phenol as a neurolytic agent: a review. Pain 1978;5:205–29.
13. Mehta M. Intractable pain. In: Mushin WW, ed. Major problems in anaesthesia. Philadelphia: WB Saunders, 1973:52–60.

ANESTH ANALG
1982;61:49-52

Spinal Anesthesia with Hyperbaric Bupivacaine: Effect of Added Vasoconstrictors

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CHAMBERS, W. A., LITTLEWOOD, D. G., AND SCOTT, D. B.: Spinal anesthesia with hyperbaric bupivacaine: effect of added vasoconstrictors. Anesth Analg 1982;61:49-52.

The effect of adding 0.2 ml of 1:1000 epinephrine or 0.5 ml of 1% phenylephrine to 3 ml of 0.5% bupivacaine in 8% dextrose for spinal anesthesia was assessed in 30 patients in a double-blind study. The addition of phenylephrine gave a small prolongation of the block which was not statistically significant. Although epinephrine produced a greater prolongation, this only reached statistical significance with regard to total duration. Three patients who received solutions that contained a vasopressor had prolonged blocks, but these solutions could not be relied upon to produce consistently a clinically significant increase in duration in individual patients.

Key Words: ANESTHETIC TECHNIQUES, Spinal.

FOR MANY YEARS vasopressors have been added to local anesthetic solutions in an attempt to prolong the duration of sensory loss. However, in the case of spinal anesthesia, the dosages recommended and the results reported vary widely. In a previously reported study (1) we found no clinically useful prolongation of spinal anesthesia using 1.5 ml of 5% lidocaine in 7.5% dextrose with the addition of up to 0.3 ml of 1:1000 epinephrine. We chose a short-acting agent for our initial study because we hoped that any differences in duration which we observed would be more obvious than with a long-acting agent. However, in clinical practice it is more relevant to determine the effects of vasopressors on longer-acting agents.

Bupivacaine hydrochloride, a solution that is virtually isobaric, has been used widely for spinal anesthesia, particularly in Germany (2-4). It consistently produces good anesthesia and has a duration of action comparable to tetracaine (5). Most investigators have used between 3 and 4 ml of a 0.5% solution although some studies have reported the use of higher concentrations (3) or larger volumes (6).

Bupivacaine in hyperbaric solution has recently been investigated as a spinal anesthetic agent. In 8% dextrose it consistently produces good anesthesia and the use of a 0.75% solution offers no significant advantage compared with a 0.5% solution (7, 8). When administered to a supine patient, 2 to 4 ml of 0.5% bupivacaine in 8% dextrose will produce sensory loss to around T-4. Increasing the volume within this range does not affect the extent of sensory loss but produces an increase in duration.

There have not been any properly controlled trials reporting the effects of added vasoconstrictors on spinal anesthesia with bupivacaine. Ramaioli and Pagani (9), in an open clinical assessment, reported durations of up to 8 hours using up to 8 ml of 0.5% bupivacaine with 0.5 mg of epinephrine. Moore (10) found that the addition of 0.2 mg of epinephrine to a solution of 0.75% bupivacaine in 8.25% dextrose produced a significant prolongation. However, in that study several variables were not properly controlled.

In view of this we carried out the following study to assess the effects of the intrathecal administration of 3 ml of 0.5% bupivacaine in 8% dextrose either alone or with the addition of either 0.2 ml of 1:1000 epinephrine or 0.5 ml of 1% phenylephrine.

Methods

Thirty male patients between 50 and 80 years of age took part in the study. All were about to undergo transurethral resection of the prostate under spinal anesthesia and all gave informed consent for the

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Received from the Department of Anaesthetics, Royal Infirmary, Lauriston Place, Edinburgh, EH3 9YW, Scotland. Accepted for publication September 10, 1981.

investigation which was approved by the hospital ethical committee.

Approximately 1 hour after premedication with oral diazepam (10 mg) an intravenous infusion was started. A lumbar puncture was performed using a 22-gauge needle at the L3-4 intervertebral space with the patient sitting. Once a free flow of cerebrospinal fluid was obtained, the test solution was injected at a rate of 1 ml every 5 seconds. After the injection, 0.5 ml of cerebrospinal fluid was aspirated and reinjected in order to confirm correct placement of the needle tip. Patients received 3 ml of 0.5% bupivacaine in 8% dextrose either alone, or with the addition of 0.2 ml of epinephrine 1:1000 or 0.5 ml of 1% phenylephrine. Ten patients received each solution. The solution used in each case (determined from a random list) was known only to the anesthetist (D.G.L.) performing the anesthesia.

After receiving the injection the patient remained sitting for 2 minutes and was then turned passively to the supine position. Ten minutes after receiving the injection the patient was placed in the lithotomy position and, depending on the level of the anesthesia, surgery commenced between 15 and 30 minutes after injection. Another anesthetist (W.A.C.) who had not been present during the injection and was unaware of the solution used, assessed the spread and duration of sensory and motor loss and recorded heart rate and arterial pressure. Sensory loss was assessed using a short bevel, 22-gauge needle and was tested on the trunk 8 to 10 cm on either side of the midline and also in the perineum and on the legs. Anesthesia was defined as the loss of the sensation of light touch and analgesia as the loss of the sensation of pinprick. Motor block was assessed by asking the patient to move his legs, using the following scale: 0, able to raise extended leg; 1, unable to raise extended leg; 2, unable to flex knee; 3, unable to flex ankle.

Assessments were made 2, 5, 10, 15, 20, 25, and 30 minutes after injection. All patients lay awake resting quietly during the operative procedure and it was possible to obtain further assessments at 15-minute intervals until no sensory loss was demonstrable.

Results were analyzed using the Student's *t*-test and Wilcoxon's rank sum test as appropriate; $p < 0.05$ was taken to indicate a statistically significant difference.

Results

The mean age of the 30 patients was 64.6 years, their mean weight 79.1 kg, and their mean height 173.6 cm. There were no significant differences between the mean ages, weight, or heights in the three groups. The mean maximum cephalad spread of sensory loss in each of the groups was similar; mean levels of analgesia and anesthesia were around T-8 and T-10, respectively (Table 1).

The mean times until the block had regressed two segments and four segments below maximum were not significantly different in the groups. Sensory loss at T-12 was last detectable an average of 104 ± 9.1 (SEM) minutes after injection in patients who received the plain solution, 119 ± 13.9 minutes after injection in patients who had received the solution containing epinephrine, and 138 ± 15.5 minutes after injection in patients who had received the solution with epinephrine (Table 2). These differences are not statistically significant.

The figure illustrates the mean duration of analgesia at different segmental levels with the three solutions. The times until anesthesia and analgesia were no

TABLE 1

Maximal Spread of Sensory Loss*

	Solution used		
	Plain solution	With phenylephrine	With epinephrine
Analgesia	8.4 ± 0.4	7.3 ± 0.8	7.5 ± 0.6
Anesthesia	10.9 ± 0.5	9.7 ± 1.0	10.2 ± 0.9

* Values are means ± SEM.

TABLE 2

Times (min) to Tw-Segment and Four-Segment Regression of Sensory Loss and Mean Durations in Thoracic Segments*

	Solution used		
	Plain solution	With phenylephrine	With epinephrine
Analgesia			
2-segment regression	81 ± 6.4	87 ± 4.9	80 ± 5.9
4-segment regression	105 ± 7.4	116 ± 8.1	117 ± 10.4
Latest time thoracic	104 ± 9.1	119 ± 13.9	138 ± 15.5
Anesthesia			
2-segment regression	80 ± 5.9	87 ± 5.4	84 ± 9.0
4-segment regression	101 ± 8.4	110 ± 4.5	120 ± 14.3
Latest time thoracic	75 ± 9.0	98 ± 12.0†	107 ± 16.1†

* Values are means ± SEM.

† n = 9; one patient in each of these groups did not develop anesthesia in thoracic segments.

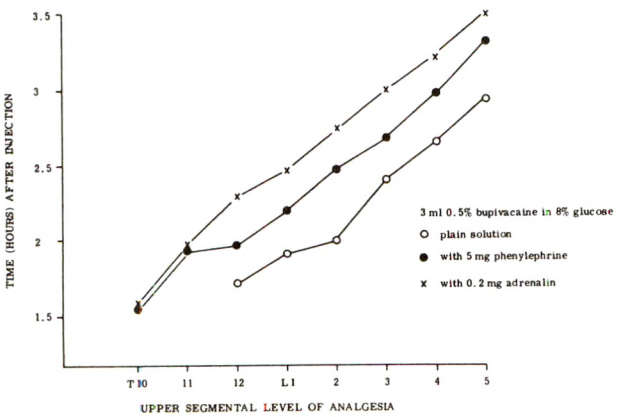


FIGURE. Mean duration of analgesia at different segmental levels.

longer detectable and until motor block had returned to degree 0 are shown in Table 3. The differences in results when the plain solution was used and when the epinephrine-containing solution was used are significantly different (Wilcoxon's rank sum test; $p < 0.05$).

No differences were apparent with regard to cardiovascular changes in the three groups. The mean maximum decrease in systolic pressure was approximately 20% in each of the groups and the maximum changes in heart rate ranged from +25% to −15% in individual cases. No patients required treatment with systemic vasopressors on account of hypotension. The maximal cardiovascular changes due to the spinal block were always apparent within 20 minutes of injection.

Eight patients who had received the plain solution developed degree 3 motor block, compared with nine patients in each of the other groups. One patient given epinephrine did not develop motor block beyond degree 0, and three patients (two in the group given no vasoconstrictors and one in the group given phenylephrine) developed partial motor block.

Discussion

Neither epinephrine nor phenylephrine affected height or degree of sensory or motor loss. Both agents increased duration at various segmental levels, but these only reached statistical significance with regard to total duration with the epinephrine-containing solution. The increase was greater with epinephrine than with phenylephrine, a finding contrary to a previous study that used tetracaine and found that phenylephrine produced greater prolongation (11).

Three patients who received solutions that contained a vasoconstrictor (two epinephrine, one phenylephrine) had prolonged blocks—total durations of 390, 315, and 285 minutes—and these cases contributed in large measure to the differences in mean duration between the groups. In our previous paper (1) we drew attention to the importance of careful standardization in studies such as this. Previously the literature has generally agreed that intrathecal vasoconstrictors substantially prolong the duration of spinal anesthesia, and it may be that clinicians have obtained this clinical impression because in a few instances they do indeed produce a large increase in duration. The results of this study indicate, however, that the addition of epinephrine to solutions of 0.5% bupivacaine in 8% dextrose produces only a small increase in mean duration and that such prolongation cannot reliably be reproduced in individual cases. The addition of phenylephrine to this preparation of bupivacaine does not appear to be justified.

Both of the studies that we have carried out to assess the effects of vasoconstrictors have involved the use of solutions containing relatively high concentrations of dextrose (7.5% and 8%). It is possible that this may alter the effect of an added vasoconstrictor and it would be interesting to repeat the study using solutions of bupivacaine without dextrose. Most of the previous studies reporting a significant prolongation of spinal anesthesia have concerned the use of tetracaine or procaine. It may be that vasoconstrictors have different effects on different local anesthetic agents when these are administered intrathecally.

TABLE 3

Durations (min) of Sensory Loss and Time until Motor Block Regressed to Degree 0*

	Solution used		
	Plain solution	With phenylephrine	With epinephrine
Analgesia	197 ± 10.8	221 ± 11.4	231 ± 24.6
Anesthesia	161 ± 11.4	181 ± 13.1	185 ± 24.4
Motor	122 ± 11.7	147 ± 16.3	163 ± 19.3†

* Values are means ± SEM.

† n = 9; one patient in this group did not develop motor block beyond degree 0.

REFERENCES

1. Chambers WA, Littlewood DG, Logan MR, Scott DB. Effect of added epinephrine on spinal anesthesia with lidocaine. Anesth Analg 1981;60:417–20.
2. Nolte H, Schikor K, Gergs P, Meyer J, Stark P. Zur frage der Spinalanesthesie mit isobarem Bupivacain 0.5%. Anaesthetist 1977;26:33–7.
3. Nolte H, Stark P. Die Dosis-Wirkungsrelation des isobaren Bupivacain zur Spinalanesthesie. Regionale-Anesthesie 1977;2: 1–4.

4. Kortum K, Rossler B, Nolte H. Morbiditat nach Spinalanesthesie. Regionale-Anesthesie 1977;2:5–11.
5. Lanz E, Schellenberg B, Theiss D. Isobare Spinalanesthesie mit Bupivacain und Tetracain. Regionale-Anesthesia 1979;2:25–31.
6. Hengesbach B, Matthes H. Ausbreitung und Wirkungen von 0.5% igem Bupivacain nach subarachnoidaler application. Med Welt 1977;28:328–30.
7. Chambers WA, Edstrom HH, Scott DB. Effect of baricity on spinal anesthesia with bupivacaine. Br J Anaesth 1981;53:279–82.
8. Chambers WA, Littlewood DG, Edstrom HH, Scott DB. Spinal anaesthesia with hyperbaric bupivacaine: the effect of dose and volume administered Br J Anaesth (in press 1982).
9. Ramaioli F, Pagani I. Nostra experienza sull impiego della bupivicaina all'1% imperbarica in 321 rachianestesie per interventi di chirurgia ortopedica e traumatologica. Minerva Anestesiol 1972;38:1–12.
10. Moore DC. Spinal anesthesia: bupivacaine compared with tetracaine. Anesth Analg 1980;59:743–50.
11. Meagher RP, Moore DC, Devries JC. Phenylephrine: the most potent potentiator of tetracaine spinal anesthesia. Anesth Analg 1966;45:134–9.

Procainamide-Induced Ventricular Tachycardia

Seven cases of procainamide-induced polymorphous ventricular tachycardia are presented. Polymorphous ventricular tachycardia is a variety of ventricular tachycardia characterized by ventricular polymorphy and changing heart rates. In four patients, polymorphous ventricular tachycardia appeared after intravenous administration of 200 to 400 mg of procainamide for the treatment of sustained ventricular tachycardia. In the remaining three patients, procainamide was administered orally for treatment of chronic premature ventricular contractions or atrial flutter. These patients had Q-T prolongation and recurrent syncope due to polymorphous ventricular tachycardia. In four patients, the arrhythmia was rapidly diagnosed and treated with disappearance of further episodes of the arrhythmia. In two patients, the arrhythmia degenerated into irreversible ventricular fibrillation and both patients died. In the seventh patient, a permanent ventricular pacemaker was inserted and, despite continuation of procainamide therapy, polymorphous ventricular tachycardia did not recur. These seven cases demonstrate that procainamide can produce an acquired prolonged Q-T syndrome with polymorphous ventricular tachycardia. *(Strasberg B, Sclarovsky S, Erdberg A, et al: Procainamide-induced polymorphous ventricular tachycardia. Am J Cardiol 1981;47:1309–14)*

ANESTH ANALG
1982;61:53-5

Inadvertent Change of Volatile Anesthetics in Anesthesia Machines

Joannes H. Karis, MD,* and Daniel B. Menzel, PhD†

KARIS, J. H., AND MENZEL, D. B.: Inadvertent change of volatile anesthetics in anesthesia machines. Anesth Analg 1982;61:53-5.

Each month for 4 months, the contents of the enflurane and halothane vaporizers of 25 North American Dräger anesthesia machines were analyzed for enflurane and halothane by gas liquid chromatography. On five occasions a mixture of the two agents was found in a vaporizer. Such a mixture may lead to the unknowing delivery of markedly different anesthetic concentrations than expected and may endanger the patient. Analysis of the contents of 35 vaporizers of Ohio and Foregger machines did not show any case of accidental filling with the wrong agent. The vaporizers of the Ohio and Foregger machines are conspicuously different in appearance and location, while the similar appearance of the two vaporizers of the Dräger machine may have contributed to the mistakes in filling. We conclude that standard-keyed filling devices for volatile anesthetics are desirable.

Key Words: EQUIPMENT: vaporizers.

THE American National Standards Institute (1) advocate in their standard for anesthetic equipment that "the filling mechanism of the vaporizer should be fitted with a permanently attached standard keyed filling device to prevent accidental filling with the wrong agent." We were interested in finding out how frequently erroneous filling of a vaporizer would occur in a large institution with an anesthesia staff of approximately 120 of which 40% are students. In addition we wanted to know whether the incidence would be similar with all types of anesthesia machines and we wished to assess the potential hazard to patients if the wrong agent was given.

Methods

Before moving to a new surgical facility, halothane and enflurane from vaporizers of 18 machines (five Ohio, 12 Foregger, and one Dräger) were sampled. Five microliters of vapor was drawn out of the container holding the sample and injected into a Varian 3700 gas chromatograph fitted with a 6-ft column containing 10% SP 2100 on Chromsorb G-HB (80/100), and the percentages of halothane and enflurane in each sample were determined. Four months later 31 vaporizers of the aforementioned machines were still in use and their contents were again sampled.

American Dräger machines fitted with concentration-calibrated ("Tec-type") Vapor-19 vaporizers were the only machines used in the new operating suite. The contents of 50 vaporizers were sampled once a month for 4 months and the halothane and enflurane concentrations determined as above.

In another series of experiments a Quantiflex "kettle-type" and a Ohio "Tec-type" enflurane vaporizer were filled with mixtures of halothane and enflurane in ratios of 1/1, 1/3, and 3/1. The concentrations of anesthetics delivered at a 5-L flow were measured by injecting 0.2 ml of the gas mixture into the gas chromatograph.

Finally, several commonly used types of vaporizers were drained and flushed with oxygen for several hours to empty them completely of all liquid anesthetic. The vaporizers were then refilled with a known volume and drained once more, forcing as much liquid out as possible by flowing oxygen through them for 2 minutes. The amount retained was the difference between the volume of anesthetic used for filling and the drained volume.

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Supported in part by National Institute for Occupational Safety and Health (NIOSH) grant 5 R01 OH00781-03.
Received from the Departments of Anesthesiology, Pharmacology, and Medicine, Duke University Medical Center, Durham, North Carolina. Accepted for publication September 15, 1981.
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Results

All samples drawn from the anesthesia machines in the old operating rooms were shown to contain pure halothane or enflurane. After the new Dräger anesthesia machines had been used for 3 months two of the 50 vaporizers contained a mixture of the two anesthetics. Checks done 1, 2, and 3 months later revealed at each time one additional instance of contamination. (The vaporizers were drained only when contamination was shown with the gas chromatographic determinations.)

When a "Tec-type" or "kettle-type" vaporizer was filled with a mixture of halothane and enflurane there was little difference in the concentrations of halothane and enflurane delivered by either of the vaporizers (Table 1). However, note that if, for example, halothane was added to an enflurane vaporizer so that a mixture of 25% enflurane and 75% halothane resulted, the patient would have received 0.33% enflurane, plus 1.37% halothane. This mixture has a MAC value approximately 3 times greater than that of the 1% enflurane which would be expected to be delivered.

While preparing for these experiments, the time required to empty a vaporizer to the point at which only trace amounts were delivered was also recorded. Fig 1 shows the concentration of halothane measured after a Fluotec vaporizer and a Quantiflex-kettle were drained of all liquid halothane, and the machines were then set to deliver 2% halothane at a 5-L flow. The Fluotec vaporizer produced above 1% halothane for more than 3 hours, 4 times as long as the Quantiflex vaporizer did. This finding correlated with the amount of halothane retained after filling and immediately draining each type of vaporizer. Table 2 lists the retained volumes of several commonly used vaporizers.

TABLE 1

Enflurane and Halothane (%) Delivered from Vaporizers Containing Both Agents

Mixture of enflurane/halothane used	Ohio calibrated vaporizer* delivered		Quantiflex kettle† delivered	
	Enflurane	Halothane	Enflurane	Halothane
	%			
75%/25%	0.81	0.43	0.88	0.56
50%/50%	0.56	1.0	0.62	1.00
25%/75%	0.33	1.37	0.34	1.25

* At 5-L flow and a 1% setting.

† At a total flow of 5 L and a calculated delivery of 1% enflurane.

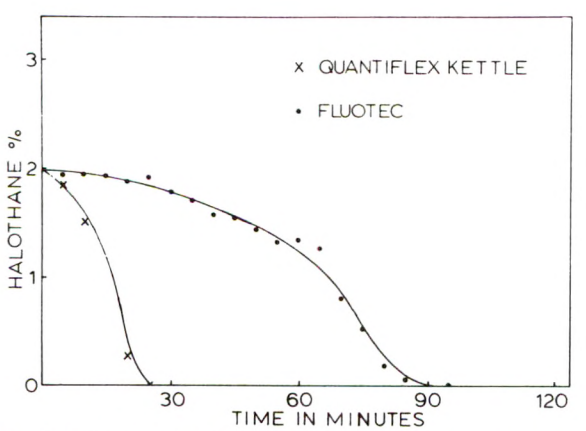


FIG 1. Time course of halothane concentration delivered from Fluotec vaporizer and from Quantiflex "kettle-type" vaporizer. Both vaporizers were at time zero completely drained, and set to deliver 2% halothane at a 5-L flow.

Discussion

No erroneous filling of "kettle-type" Ohio and Foregger machines with halothane and enflurane could be documented. (Although only two determinations were done, amounts detectable with a gas chromatograph could be expected to persist for many weeks.)

The Dräger Vapor-19 vaporizers for enflurane and halothane (Fig 2) are of the same external configuration that led in five documented instances to filling with the wrong agent. This can cause a higher or lower than expected anesthetic concentration as well as the delivery of an agent not chosen or desired by the anesthesiologist. This suggests that, at least in a large institution with many students, a "keyed" system would be desirable. Unfortunately keyed systems have not been widely accepted, perhaps because of the design of the systems commercially available. Many anesthesiologists find them cumbersome and spillage of the agents is said to be common. We believe the search for a universally acceptable keyed system should continue, but in the meantime (or in addition) the vaporizer and the anesthetic agent bottle

TABLE 2

Volume Retained in Each Vaporizer after Ostensibly Complete Drainage of Anesthetic

Vaporizer	Retained volume
	ml
Fluotec	32
Dräger Vapor-19	55
Ohio-Ethrane vaporizer	89
Ohio 130-ml Vernitrol	5
Foregger 150-ml kettle	6
Quantiflex kettle	12

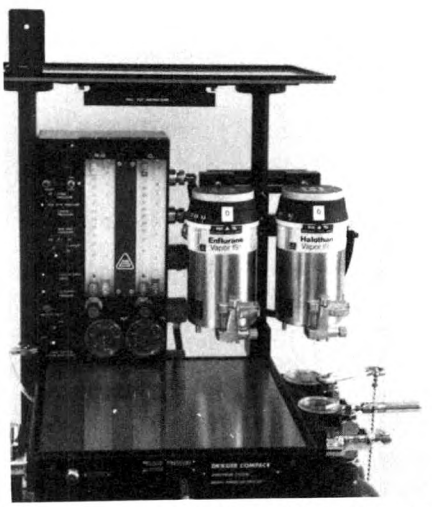


FIG 2. Dräger anesthesia machine with two vaporizers, one for halothane and one for enflurane, of identical appearance and placed next to each other.

should be clearly color coded. Our observation that use of vaporizers that are conspicuously different in appearance (Fig 3) is associated with fewer mistakes, appears to support such a contention.

It is often suggested that isoflurane can be used in a concentration-calibrated halothane vaporizer. We showed that concentration-calibrated vaporizers, because of their built-in wicks, can retain considerable amounts of anesthetics after complete drainage. Anesthesiologists should be warned to fill a vaporizer with another agent only after flowing oxygen through it for several hours following complete drainage. The contents of the vaporizer should in addition be clearly marked.

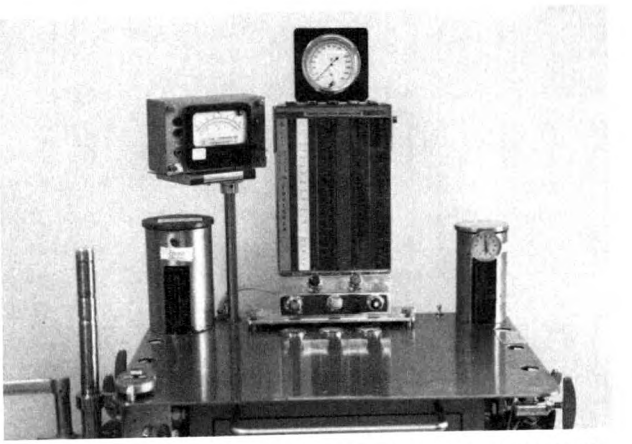


FIG 3. Foregger anesthesia machine with small copper kettle placed on the left for halothane and larger kettle on right for enflurane. Flow meters for each kettle are on extreme left and right, respectively.

In summary, volatile anesthetics may be added to the wrong vaporizer because of inattention of the anesthesiologist, the lack of a keyed system, and use of vaporizers and drug bottles that are not distinctly different. The incidence of such errors was documented in an educational institution, and such errors could lead to exposure of patients to incorrect agents and anesthetic concentrations. The use of a keyed system, color coding, or both may help to prevent these mistakes.

Because large volumes of anesthetic may be retained, especially in concentration-calibrated vaporizers, prolonged flushing with oxygen is required before filling the vaporizer with another agent.

REFERENCE

1. American National Standard minimum performance and safety requirements for components and systems of continuous flow anesthesia machines for human use. American National Standards Institute, Inc, New York: Feb 20, 1979.

technical COMMUNICATION

True Oil/Water Partition Coefficients of Procaine and Lidocaine and Estimation of Their Dissociation Constants in Organic Solvents

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The potencies of anesthetics are often discussed in relation to the lipid solubility expressed by oil/water partition coefficients. It has been demonstrated that the biologic activities of a number of drugs unrelated to anesthetics also can be expressed by a primary function of their lipophilicity or hydrophobicity derived from oil/water partition coefficients [see, for instance, Hansch and Clayton (1)].

The values of oil/water partition coefficients vary by the choice of the organic solvents for the oil phase. Octanol is probably most often used for the oil phase. It has been generally accepted that octanol represents the physical properties of the biologic membrane rather well (1). Nevertheless, other organic solvents are also used and there have been a number of attempts to correlate the different values among different organic solvents to derive a unified parameter for the lipophilicity or hydrophobicity (1–8) although these two terms are not identical and are not well defined. The term "lipophilicity" is tentatively used in the present article to describe the property expressed by oil/water partition coefficients.

The clinically used local anesthetics contain dissociable amine moiety at one end of the molecule and protonated charged molecules and uncharged base molecules coexist at the physiologic pH. Although it is generally assumed that charged molecules do not partition into the oil phase, the oil/water partition coefficients of local anesthetics are often measured [see, for instance, Covino and Vassallo (9)] at near physiologic pH. Therefore, the obtained value is not the true partition coefficient expressed by concentration of the uncharged drug in the oil phase/concentration of the uncharged drug in the water phase, and is an apparent partition coefficient expressed by concentration of the uncharged drug in the oil phase/concentration of the uncharged drug plus charged drug in the water phase.

The present study was undertaken to establish true oil/water partition coefficients of aromatic amine local anesthetics. An ester-type local anesthetic, procaine, and an amide-type local anesthetic, lidocaine, were chosen and their oil/water partition coefficients were estimated at two pH values at which the anesthetics exist predominantly in either charged or uncharged forms. Three organic solvents, heptane, benzene, and octanol, which have different degrees of polarity, were used for the oil phase. Octanol was used because of the afore-mentioned reason and because the majority of the partition coefficient studies were performed with this solvent. Heptane was included because its tendency to exclude water molecules appeared to be one of the highest among alkanes whereas the inclusion of benzene was arbitrary. As

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Supported in part by the United States Public Health Service grant GM27670 and by the Medical Research Service of the Veterans Administration.
Received from the Department of Anesthesia, University of Kansas Medical Center, College of Health Sciences and Hospital, Kansas City, Kansas, and Anesthesia Service, Veterans Administration Medical Center, Salt Lake City, Utah. Accepted for publication September 15, 1981.
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the numerical values of the partition coefficients vary considerably according to the expressions used for the drug concentrations (10), three sets of values are presented by using mole fraction, molality, and molarity for the anesthetic concentration.

It is expected that the dissociation constants of protonated local anesthetics in nonaqueous phase are different from those in water. The present study describes a novel method to estimate the dissociation constants of these drugs in nonaqueous phases in equilibrium with water.

Theoretical Considerations

The clinically used local anesthetics are usually supplied as a salt between local anesthetic base, L, and hydrochloric acid, HCl, and the dissociation involves the following sequences.

$$\begin{array}{ccccc} L\cdot HCl & \rightleftharpoons & H^+L & \rightleftharpoons & L \\ & & \searrow & & \searrow \\ & & & + Cl^- & + H^+ \end{array} \quad (1)$$

By designating K_a for the dissociation constant of H^+L, the following equations are obtained:

$$H^+L \rightleftharpoons H^+ + L \quad (2)$$

$$K_a = \frac{[H^+][L]}{[H^+L]} \quad (3)$$

$$pH = pK_a + \log\{[L]/[H^+L]\} \quad (4)$$

where square brackets indicate the concentrations.

For the ion-pair formation between H^+L and Cl^-, A^- is used to designate anion in general and is written

$$H^+L + A^- \rightleftharpoons AHL \quad \text{or} \quad AHL \rightleftharpoons H^+L + A^- \quad (5)$$

The uncharged forms, i.e., L and AHL, are expected to be lipid soluble, whereas H^+L is not. Although charged molecules are often considered to be completely insoluble to oils, we assume nonzero solubility for H^+L into organic solvents. When the water and oil phases are expressed by subscripts w and o, respectively, and assuming the activity coefficient of each component to be unity at dilute concentrations, the apparent partition coefficient, P_{app}, is written

$$P_{app} = \frac{[AHL]_o + [H^+L]_o + [L]_o}{[AHL]_w + [H^+L]_w + [L]_w} \quad (6)$$

The true partition coefficients for each species are defined as

$$P_L = [L]_o/[L]_w \quad (7)$$

$$P_{HL} = [H^+L]_o/[H^+L]_w \quad (8)$$

$$P_{AHL} = [AHL]_o/[AHL]_w \quad (9)$$

In aqueous solutions in which L and H^+L coexist, the concentration of AHL is near zero due to the high dissociation constant of the local anesthetic HCl salt. In this case the ratio between [L] and $[H^+L]$ becomes from equation 4 as

$$\begin{aligned} \log\{[L]_w/[H^+L]_w\} &= pH - pK_a \\ [L]_w/[H^+L]_w &= 10^{(pH-pK_a)} \end{aligned} \quad (10)$$

For convenience, the ratio between uncharged and charged species is expressed by α

$$10^{(pH-pK_a)} = \alpha$$

then

$$[L]_w = \alpha[H^+L]_w \quad \text{or} \quad [H^+L]_w = \alpha^{-1}[L]_w$$

When the pH of the aqueous solution of a local anesthetic is higher than the pK_a by at least 2 pH units, less than 1% of the anesthetic molecules exist in the H^+L form and the AHL form is practically nonexistent. Then the apparent partition coefficient for L, P_{app}^{L}, obtained at high pH is written

$$P_{app}^{L} = \frac{[L]_w\cdot P_L + [H^+L]_w\cdot P_{HL}}{[L]_w + [H^+L]_w} \quad (11)$$

$$= \frac{[L]_w\cdot P_L + [L]_w\cdot\alpha^{-1}\cdot P_{HL}}{[L]_w + \alpha^{-1}\cdot[L]_w} = \frac{P_L + \alpha^{-1}\cdot P_{HL}}{1 + \alpha^{-1}} \quad (12)$$

$$P_L = (1 + \alpha^{-1})P_{app}^{L} - \alpha^{-1}P_{HL} \quad (13)$$

In this equation, $P_{HL} \ll P_L$ and when $\alpha^{-1} \ll 1$, it reduces to

$$P_L = P_{app}^{L} \quad (14)$$

In cases in which the difference between pH and pK_a is less than 2 pH units, P_{app}^{L} is corrected by

$$P_L = (1 + \alpha^{-1})P_{app}^{L} \quad (15)$$

whereas the last term in equation 13 can still be omitted because $P_{HL} \ll P_L$ and $\alpha^{-1} < 1$.

By similar treatment, the true partition coefficient for the charged species is related to the apparent partition coefficient for H^+L, P_{app}^{HL}, measured at pH values less than pK_a as

$$P_{HL} = (1 + \alpha)P_{app}^{HL} - \alpha P_L \quad (16)$$

When the difference between pH and pK_a is larger

than 2 pH units, α becomes less than 0.01 and the term $(1 + \alpha)$ can be neglected.

$$P_{HL} = P_{app}^{HL} - \alpha P_L \quad (17)$$

In this case, however, αP_L term can no longer be ignored. If P_L is in the order of 100-fold of P_{HL}, the pH should be adjusted 4 pH units less than the pK_a value in order to suppress the effect of the last term to the true partition coefficient within 1%. If the difference between P_L and P_{HL} is in 3 orders of magnitude, 5 pH units less than the pK_a is required for the above purpose. The strongly acidic conditions would increase the concentration of AHL and increase the apparent partition coefficient. It is apparent that correction for the ion-pair formation becomes necessary.

Therefore, the strategy of the present experiment was first to obtain P_L at pH values at approximately 2 pH units greater than the pK_a values. The obtained P_L value was used to correct the apparent partition coefficient of the charged species measured at approximately 2 pH units less than the pK_a. Extremely low pH conditions were avoided and anion concentrations were kept minimum by omitting buffer salts in order to prevent the tendency to form the ion-pair, AHL.

Another source of error for the estimation of the true partition coefficient is dimerization of the local anesthetics. The affinity potentials of the self-association of local anesthetics at air/water interface have been estimated (11), and formation of the micellar aggregate was reported (12). Fernandez (12) estimated the critical micelle concentration of tetracaine to be approximately 0.07 M. Infrared spectroscopic studies also revealed hydrogen bonding for a number of local anesthetics (13). The present study was performed at the local anesthetic concentration less than $5 \cdot 10^{-4}$ M to avoid polymerization. The partition coefficients were measured at several concentrations less than $5 \cdot 10^{-4}$ M to examine whether the value remains constant.

Estimation of the apparent and true partition coefficient of AHL was not attempted in the present study because: (*a*) AHL probably has little significance for the action of local anesthetics at physiologic conditions, and (*b*) the direct estimation is difficult as the dissociation constant of this species is unknown and the titration has to be performed in a strongly acidic condition.

Methods and Materials

Uniformly [^{14}C]labeled procaine (specific activity: 47 mCi/mmol) and lidocaine (specific activity: 30 mCi/mmol) were obtained from New England Nuclear Corporation. Nonradioactive procaine and lidocaine were gifts from Sterling-Winthrop Research Institute and Astra Pharmaceutical Products, Inc., respectively. Octanol, benzene, and heptane were the highest grades available from MCB (Gibbstown, NJ) and used without further purifications.

Water was first distilled, then purified by a Millipore system which consisted of an activated charcoal column, two mixed-bed ion-exchanger columns, and an ultrafilter. The specific resistivity of water was maintained at better than 16 Mohm/cm, and contamination by surface active impurities was checked by a dynamic surface tension balance. A 10 to 1 compression of the surface of the obtained water, after being left 10 minutes, was confirmed to produce less than 0.1 dyne/cm change of the surface tension. The organic solvents were equilibrated with water at temperatures at which the partition study was performed.

The radioactive local anesthetics were dissolved in water equilibrated by the organic solvents with carrier nonradioactive drugs at several concentrations. The maximum concentration was 0.5 mM. It was found that identical values were obtained for the partition coefficient regardless of the anesthetic concentrations within the present experimental condition. The result indicated absence of significant polymerization of the anesthetics at the concentrations used in the present study.

An aliquot of 1.0 ml of local anesthetic solution was mixed with 1.0 ml of the organic solvents (equilibrated with water) in a stoppered Erlenmeyer flask and mixed in a temperature-controlled shaker for 1 hour. The temperature was monitored by a thermistor thermometer (United Systems, Dayton, OH) with 0.01 C resolution.

After separation of the two phases, the radioactivity of the two phases was measured by transferring 0.1 ml of each phase into counting cocktail 3a70B (Research Product International Corporation, Elk Grove Village, IL). The radioactivity was measured by a Beckman LS 3150-T liquid scintillation counter with automatic quench correction. The total count of the radioactivity of each flask was calculated by the sum of the total count of each phase obtained by multiplying the volume of the phase with each specific radioactivity. By comparing the calculated total radioactivity with that introduced into the vial, it was confirmed that the amount of local anesthetics adhering on the glass surface was negligible.

Each study was performed at two pH values, one was higher and the other was lower than the pK_a

values of the drug by approximately 2 pH units. The pH was adjusted by the addition of 0.1 M NaOH and was measured by a Corning digital pH meter with a combination glass electrode. The reported pK_a value for procaine is 8.92 and that for lidocaine is 7.86 (13, 14). In order to avoid the nonspecific alkaline hydrolysis of the ester-type local anesthetics, the partitioning process was completed within 2 hours from the pH adjustment. The pH values of the aqueous phase tend to decrease during equilibration with the organic solvents especially with lower pH values. The reading obtained after the equilibration was used to calculate the $[L]/[H^+L]$ ratio. When the pH after the equilibration was within 2 pH units from pK_a, equation 15 was used in place of equation 14 to derive true partition coefficient for the uncharged species. The true partition coefficients for charged species were calculated according to equation 17.

The thermodynamic parameters are calculated as follows. The chemical potential of ith species is written by using mole fraction

$$\mu_i = \mu_i^0 + RT \ln(X_i f_i) \tag{18}$$

where μ_i^0 is the standard chemical potential represented by the mole fraction (X_i) and f_i is the activity coefficient.

As the chemical potential of the solute (anesthetics) in water is equal to that in the organic phase at partition equilibrium,

$$\Delta G^0 = \mu_{i(o)}^0 - \mu_{i(w)}^0 = -RT \ln K \tag{19}$$

The standard molar enthalpy change, ΔH^0, and entropy change, ΔS^0 of the transfer were calculated from the temperature dependence of the free energy of transfer according to the Gibbs-Helmholtz equation

$$\Delta G^0 - \Delta H^0 = T(\partial \Delta G^0 / \partial T) = -T\Delta S^0 \tag{20}$$

Results

Both anesthetics showed higher oil/water partition coefficients with more watery polar solvent than oily apolar solvent as shown in Table 1. As partition coefficient assumes different values (10) according to the units of concentration, the values obtained from mole fraction (number of moles of anesthetics/total number of moles in the solution), molality (moles of anesthetics/1000 g of the solvent), and molarity (moles of anesthetics/1000 ml of the solution) are presented. The conversion factors among these values were calculated according to equation 21 from Kamaya et al (10) using the following density values (15): benzene 0.87865, heptane 0.68376, and octanol 0.8270, at 20 C. With each solvent, the unchanged species were more soluble in the oil phase than the charged species as expected.

From the thermodynamic relationship between the equilibrium constant calculated from mole fraction and the standard molar free energy change of the transfer, ΔG^0, the standard molar enthalpy change, ΔH^0, and the standard molar entropy change, ΔS^0, were estimated according to equation 20 and the values are shown in Table 2.

Discussion

The present results confirmed the general assumption that uncharged molecules are more lipid soluble than the charged counterparts. It is also clear that the oil/water partition coefficient of local anesthetics differs a great deal depending on the polarity of the solvent used for the oil phase. Both species of both anesthetics partitioned more into octanol than heptane. In spite of the general impression of the term "lipophilicity," these anesthetics preferred polar solvent over apolar solvent.

TABLE 1

Oil/Water Partition Coefficients of Charged and Uncharged Species of Lidocaine and Procaine at 23 C between Three Organic Solvents (Heptane, Benzene, and Octanol)/Water Computed from Concentrations Expressed by Mol Fraction (P), Molality ($P_{(m)}$), and Molarity ($P_{(c)}$)

	Charged			Uncharged		
	P	$P_{(m)}$	$P_{(c)}$	P	$P_{(m)}$	$P_{(c)}$
Lidocaine						
Heptane	0.826	0.149	0.102	72.5	13.0	8.93
Benzene	15.4	3.54	3.19	110.0	25.3	22.2
Octanol	26.8	3.71	3.07	572.0	79.1	65.5
Procaine						
Heptane	0.053	0.0096	0.0065	5.25	0.944	0.647
Benzene	0.675	0.156	0.137	84.8	19.5	17.2
Octanol	2.39	0.331	0.274	243.0	33.6	27.8

TABLE 2

Standard Molar Free Energy Change ($\Delta G°$) at 23 C, Enthalpy Change ($\Delta H°$), and Entropy Change ($\Delta S°$) Due to Transfer of Charged and Uncharged Species of Lidocaine and Procaine from Water to Organic Solvents*

	$\Delta G°$	$\Delta H°$	$\Delta S°$	Partition coefficient† (n = 6)
	kcal/mol		*cal/mol/deg*	
Lidocaine				
Heptane				
Charged	0.112	6.09	20.2	0.826 ± 0.021
Uncharged	−2.52	2.63	17.4	72.5 ± 1.2
Benzene				
Charged	−1.61	2.63	14.3	15.4 ± 0.8
Uncharged	−2.77	1.08	13.0	110 ± 2.1
Octanol				
Charged	−1.94	3.17	17.3	26.8 ± 0.9
Uncharged	−3.74	0.69	15.0	572 ± 11
Procaine				
Heptane				
Charged	1.72	7.51	19.6	0.063 ± 0.004
Uncharged	−0.98	2.89	13.1	5.25 ± 0.27
Benzene				
Charged	0.23	4.32	13.8	0.675 ± 0.048
Uncharged	−2.61	1.10	12.5	84.8 ± 1.7
Octanol				
Charged	−0.51	3.59	13.9	2.39 ± 0.16
Uncharged	−3.23	0.86	13.8	243 ± 4.0

* Partition coefficients (23 C, mole fraction) are also shown.
† Values are means ± SD.

There is no single parameter to express the oiliness of organic solvents. However, for convenience, we shall use dielectric constant of the solvent as an indicator of the oiliness. Dielectric material has a relatively low electrical conductivity, and the dielectric constant is defined as the ratio of the capacity of a condenser with that material to the capacity of the same condenser with a vacuum for dielectric. The dielectric constants for heptane, benzene, and octanol are 1.9, 2.3, and 10.3, respectively (15) at 20 C. The smaller number signifies that the solvent is more oily and vice versa. In comparison, the dielectric constant of water is approximately 80 at 20 C.

Both local anesthetics, even in the uncharged form, showed low partition coefficients to heptane. For uncharged procaine, the value of the partition coefficient estimated from molarity was 0.647, and for the uncharged lidocaine, it was 8.93. The partition coefficients to octanol were larger, and the values were 27.8 for uncharged procaine and 65.5 for uncharged lidocaine.

We (16) have previously reported that the molarity partition coefficients of uncharged molecules of lidocaine and procaine between dipalmitoylphosphatidylcholine bilayer membrane and water were 76 and 159, respectively. The value for lidocaine agrees favorably with that of the present octanol/water partition coefficient where $P_{(c)}$ (partition coefficient obtained from molarity) is 63.3, but the values for procaine are quite different between the two (159 vs 27.8). It implies that the physical property of the binding site of procaine at the membrane is unlike that of octanol. Presumably, the site of adsorption of procaine at the membrane surface may be strongly inclined toward the aqueous phase.

The ordering of water molecules at an interface is well known. Bockris et al (17) reported that the dielectric constant of the first layer of water molecules next to a surface is approximately 6 and that of the second layer is 32. The present results suggest that the local anesthetic molecules may be adsorbed to the membrane interface near the structured water region at which the dielectric constant is optimal for the solvation of these molecules.

The temperature dependence of the partition coefficient showed positive ΔH. It indicates that enthalpy does not favor the transfer of the anesthetics from water to oil phase. In order for a reaction to proceed spontaneously, ΔG must be negative. The transfer of anesthetics into the organic solvents was accomplished by the large positive entropy change overcoming the positive enthalpy change. Thus penetration of local anesthetics into the oil phase is an entirely entropy-driven process.

The dissociation constant of protonated local anesthetics in nonaqueous phase is now considered,

$$H^+L_o \rightleftharpoons H^+_o + L_o \tag{21}$$

$$K_a^0 = \frac{[H^+]_o[L]_o}{[H^+L]_o} \tag{22}$$

$$pH^0 = pK_a^0 + \log([L]_o/[H^+L]_o) \tag{23}$$

where pH^0 is the negative logarithm of the proton activity in the nonaqueous phase and pK_a^0 is the negative logarithm of the dissociation constant of H^+L in the nonaqueous phase in equilibrium with water.

When the ratio between uncharged and charged species in the organic phase is expressed by β

$$10^{(pH^0 - pK_a^0)} = \beta$$

then

$$[L]_o = \beta[H^+L]_o \quad \text{or} \quad [H^+L]_o = \beta^{-1}[L]_o \tag{24}$$

As

$$[L]_o = P_L[L]_w \quad \text{and} \quad [H^+L]_o = P_{HL}[H^+L]_w$$
$$[L]_o/[H^+L]_o = \beta = P_L[L]_w/P_{HL}[H^+L]_w \tag{25}$$

TABLE 3

pK_a Values of Protonated Form of Local Anesthetics in Three Organic Solvents Equilibrated with Aqueous Solution at 23 C*

	Heptane	Benzene	Octanol	Water
Lidocaine	5.92	7.01	6.53	7.86
Procaine	6.92	6.82	6.91	8.92

* pKa values in water (14, 18) are listed for comparison.

where

$$[L]_w/[H^+L]_w = \alpha$$

Therefore

$$P_L/P_{HL} = \beta/\alpha \quad (26)$$

By taking the logarithm of both sides

$$\log(P_L/P_{HL}) = pH^0 - pK_a^0 - (pH - pK_a) \quad (27)$$

Under the convention of thermodynamics, the activities of protons in two phases in equilibrium are equal. Therefore, the activity of protons in the nonaqueous phase (pH^0) should be equal to the pH of the aqueous phase in equilibrium, and equation 27 reduces to

$$\log(P_L/P_{HL}) = pK_a - pK_a^0 \quad (28)$$

or

$$pK_a^0 = pK_a - \log(P_L/P_{HL}) \quad (29)$$

The estimated pK_a^0 values of the protonated local anesthetics in the organic solvents in equilibrium with aqueous local anesthetic solution are listed in Table 3. The results show that the pK_a values in the organic solvents are lower than those in water indicating the relative increase of the uncharged species over the charged species in the organic solvents.

REFERENCES

1. Hansch C, Clayton JM. Lipophilic character and biological activity of drugs. II. The parabolic case. J Pharm Sci 1973;62:1–21.
2. Fujita T, Isawa J, Hansch C. A new substituent constant, π, derived from partition coefficients. J Am Chem Soc 1964;86: 5175–80.
3. Seiler P. Interconversion of lipophilicities from hydrocarbon/water systems into the octanol/water system. Eur J Med Chem 1974;9:473–9.
4. Nys GG, Rekker RF. The concept of hydrophobic fragmental constants (f-values). II. Extension of its applicability to the calculation of lipophilicities of aromatic and heteroaromatic structures. Eur J Med Chem 1974;9:361–75.
5. Murray WJ, Hall LH, Kier LB. Molecular connectivity. III. Relationship to partition coefficients. J Pharm Sci 1975;64: 1978–81.
6. Armstrong NA, James KS, Wong CK. Inter-relationships between solubilities, distribution coefficients and melting points of some substituted benzoic and phenylacetic acids. J Pharm Pharmacol 1979;31:627–31.
7. McGowan JC, Ahmad P, Mellors A. The estimation of partition coefficients of steroids between water and ether. Can J Pharm Sci 1979;14:72–4.
8. Abraham MH. Free energies of solution of rare gases and alkanes in water and nonaqueous solvents. A quantitative assessment of hydrophobic effect. J Am Chem Soc 1979;101: 5477–84.
9. Covino BG, Vassallo HG. Local anesthetics: mechanism of action & clinical use. New York: Grune & Stratton, 1976:8.
10. Kamaya H, Kaneshina S, Ueda I. Partition equilibrium of inhalation anesthetics and alcohols between water and membranes of phospholipids with varying acyl chain-lengths. Biochim. Biophys Acta 1981;646:135–42.
11. Lin HC, Ueda I, Lin SH, Shieh DD, Kamaya H, Eyring H. Surface activities of tertiary amine local anesthetics at air/water interface in the presence and absence of phospholipid monolayers. Biochim Biophys Acta 1980;598:51–65.
12. Fernandez MS. Formation of micelles and membrane action of the local anesthetic tetracaine hydrochloride. Biochim Biophys Acta 1980;597:83–91.
13. Guerin M, Dumas JM, Sandorfy C. Vibrational spectroscopic studies of molecular associations by local anesthetics. Can J Chem 1980;58:2080–8.
14. Truant AP, Takman B. Differential physical-chemical and neuropharmacologic properties of local anesthetic agents. Anesth Analg 1959;38:478–84.
15. CRC Handbook of Chemistry and Physics. 60th ed. Boca Raton, FL: CRC Press, 1979.
16. Ueda I, Tashiro C, Arakawa K. Depression of phase-transition temperature in a model cell membrane by local anesthetics. Anesthesiology 1977;46:327–32.
17. Bockris JO'M, Devanathan MAV, Muller K. On the structure of charged interfaces. Proc R Soc London Ser A 1963;274:55–79.
18. DeJong RH. Local Anesthetics. 2nd ed. Springfield, IL: Charles C Thomas, 1977:45.

CLINICAL reports

Successful Resuscitation following Massive Bupivacaine Overdose

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Albright (1) reported six cases of cardiovascular collapse following the use of bupivacaine or etidocaine for local anesthesia. Cardiopulmonary resuscitation in these patients was either unsuccessful or difficult and prolonged. We report events in a patient who had grand mal seizures and ventricular tachycardia following scalp infiltration with more than 4 times the usually recommended dose of bupivacaine. Nevertheless, control of seizures and cardiac resuscitation were quickly achieved without adverse sequelae. Unusual here was the administration of lidocaine (like bupivacaine, an amide local anesthetic) to aid in conversion of ventricular tachycardia.

Case Report

A 23-year-old, 66-kg woman had refractory grand mal seizures following head injury at age 7 years. She came to surgery for electrical identification and resection of the left temporal lobe focus under local anesthesia. Previous medication including phenytoin, 400 mg daily, and phenobarbital, 60 mg twice daily, was discontinued 24 hours before surgery. Electrocardiogram (ECG), chest x-ray, and other laboratory studies were within normal limits. The electroencephalogram showed a highly active focal epileptogenic process in the left temporal lobe.

She was premedicated with intramuscular cephapirin sodium, 1 g, chlorpromazine, 75 mg, and dexamethasone, 10 mg, 1 hour before surgery. The plan was to lift a skull flap to expose the cortex for electrographic delineation of the seizure focus before excision. As general anesthetics suppress epileptiform discharges, the surgeon selected local anesthesia without sedation, with anesthesia standby.

The patient was calm and cooperative upon arrival in the operating room. Vital signs were: temperature 37.5 °C, pulse 100 beats per minute, blood pressure 110/80 torr, and respirations 14 breaths per minute. An intravenous infusion was started and ECG lead II and blood pressure were monitored. The patient was positioned in the right lateral position, and oxygen was given by nasal cannula. Rather than infiltrating 150 mg of bupivacaine as planned, the surgeon injected 150 ml of 0.5% (750 mg/l) bupivavacine without epinephrine into the shaved scalp. Approximately 6 minutes later, and before scalp incision, a grand mal seizure occurred.

Unaware of the miscalculation in bupivacaine dose, the surgeon at first assumed the patient was having a regular convulsion—hence no medication was given. Ventilation with oxygen by mask was started with the patient still on her side; ECG was obscured by muscle and movement artifacts. Convulsions continued for 3 to 4 minutes while the patient was restrained, dislodging ECG leads and blood pressure cuff. At that time, peripheral pulses could no longer be palpated. The still-convulsing patient was then quickly turned into the supine position and external cardiac compression started, with immediate return of arterial pulses. To facilitate ventilation, the trachea was intubated, aided by 100 mg of succinylcholine. After 10 mg of diazepam was administered, seizures stopped and the reconnected ECG showed ventricular tachycardia.

As cardiopulmonary resuscitation produced a palpable pulse, 54 meq of sodium bicarbonate and 175 mg of lidocaine were given intravenously. A single electrical countershock was then delivered to the heart with chest electrodes, after which the ECG showed sinus tachycardia at a rate of 145 beats per minute, with blood pressure of 100/70 torr. Arterial blood gas values included pH 7.15, P_{CO_2} 54 torr, P_{O_2} 368 torr, HCO_3^- 19 meq/L, and BE −9 meq/L. An additional 54 meq of sodium bicarbonate was given intravenously, as were calcium chloride, 1 g, phenytoin, 200 mg,

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Received from the Department of Anesthesiology, Tufts University School of Medicine, 171 Harrison Avenue, Boston, Massachusetts 02111. Accepted for publication September 6, 1981.

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and lidocaine infused at 2 mg/min. Arterial blood drawn 12 minutes following countershock, and with F_{IO_2} 1.0, showed pH 7.39, P_{CO_2} 34 torr, P_{O_2} 488 torr, HCO_3^- 20 meq/L, BE −4 meq/L, and plasma bupivacaine 1.66 μg/ml. (Because lidocaine serves as an internal standard in the bupivacaine assay, blanks were used to offset the lidocaine in our blood samples.)

On transfer to the neurosurgical intensive care unit, the ECG showed sinus rhythm at rates of 100 to 140 beats per minute, normal PR interval, and slightly depressed ST segments. A blood sample obtained at this time for measurement of creatinine phosphokinase isoenzyme levels was subsequently reported as negative for MB bands. Five hours after the ventricular tachycardia, lidocaine (total dose 600 mg) was discontinued. The patient was alert and oriented the next day with a sinus rhythm at a rate of 100 beats per minute. The ST-segment depression had resolved overnight.

One week later she returned for craniotomy under local anesthesia. She received no premedication. The scalp was infiltrated with 110 ml of 0.25% and 35 ml of 0.125% bupivacaine (318.75 mg) without epinephrine. A left temporal lobectomy was performed uneventfully, and she was discharged 5 days later.

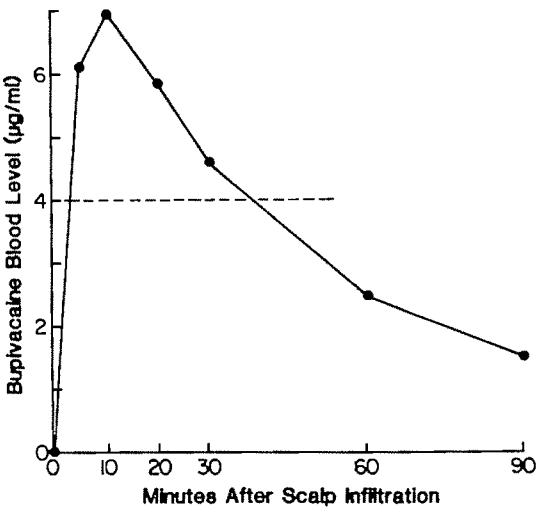


FIGURE. Estimated time profile of arterial blood concentrations of bupivacaine following infiltration of scalp with bupivacaine, 11.4 mg/kg, without epinephrine. Values computed by interpolation from figure 2 of Colley and Heavner (2), whose data are based on scalp infiltration with bupivacaine, 2.0 mg/kg, without epinephrine. Dashed line represents approximate convulsant threshold for bupivacaine (see "Discussion"), which is reached in approximately 3 minutes.

Discussion

Colley and Heavner (2) reported blood levels of bupivacaine in 10 patients whose scalps were infiltrated with plain bupivacaine for awake craniotomy (11 other subjects had epinephrine 1:400,000 added to the solution). In five patients receiving an average 1.25 mg/kg of 0.125% bupivacaine without epinephrine, Colley and Heavner found peak bupivacaine concentration in the blood to be 0.77 μg/ml; this calculates to a peak level of 0.6 μg/ml for each 1 mg/kg of bupivacaine infiltrated. In five patients receiving an average of 2.0 mg/kg of 0.25% bupivacaine without epinephrine, the peak bupivacaine concentration in the blood was 1.23 μg/ml, which also calculates to a peak level of 0.6 μg/ml for each 1 mg/kg of bupivacaine infiltrated. On the basis of these calculations we would expect that in our patient, who was given 11.4 mg/kg of 0.5% bupivacaine without epinephrine, peak blood levels of bupivacaine might be in the range of 6.9 μg/ml (Figure). In fact, this estimate may be low because the vasodilating effect of 0.5% bupivacaine without epinephrine might increase the rate of absorption and further increase the blood level (3).

Epileptics do not appear to have a heightened susceptibility to toxic reactions from local anesthetics (4). In fact, local anesthetics have been used as anticonvulsants in the treatment of grand mal epilepsy, although higher doses reactivate convulsions (5). Moore et al (6) consider the convulsant arterial plasma level of bupivacaine in man to exceed 4 μg/ml. In patients in whom arterial blood samples were collected within 1 minute of the onset of convulsions, bupivacaine levels were close to that range, namely 3.2 and 4.4 μg/ml (7). Thus the level we calculated clearly is beyond the convulsant threshold for bupivacaine. Because of the initial steep decay in postinfiltration bupivacaine blood levels (Figure), the arterial serum value of 1.66 μg/ml we obtained some 12 minutes after the convulsant peak was much lower than the above-reported convulsant levels.

Worth noting is that subsequent infiltration of the patient's scalp with nearly 320 mg of bupivacaine (4.8 mg/kg) did not precipitate convulsions, even though that dose still was close to double the usually recommended upper dose limit (2.5 mg/kg) of bupivacaine. Perhaps the surgeon "got by" this time because the corresponding calculated peak blood level of bupivacaine would be 2.9 μg/ml, or less than the presumed convulsant level in man.

In addition to high bupivacaine blood levels, the hypoxia, hypercapnia, and lactic acidosis that accompany convulsions might have contributed to our patient's cardiovascular collapse. Moore et al (7) reported that carbon dioxide production and oxygen consumption are greatly increased during local anesthetic-induced seizures. These factors, plus depres-

sion of intracardiac conduction and myocardial contractility by bupivacaine (8), readily set the stage for cardiovascular failure.

One might wonder about the advisability of using lidocaine to control arrhythmias following bupivacaine toxicity as both are amide local anesthetics and presumably bind to the same protein and lipid sites. Experimentally, cardiac arrhythmias rarely occur before or following lidocaine-induced convulsions, perhaps because of the drug's well known antiarrhythmic effects (9). In marked contrast, ventilated cats given intravenous bupivacaine consistently develop intracardiac conduction defects and ventricular arrhythmias before the onset of convulsions (10). We have found experimentally that persistent dysrhythmias following infusion of supraconvulsant doses of bupivacaine can be converted to normal sinus rhythm by one or two doses of lidocaine, 2.5 mg/kg, without altering the EEG or blood pressure (11). Whether lidocaine contributed to successful conversion of ventricular tachycardia in our case we do not know. Hodgkinson (R. Hodgkinson, personal communication, 1980), for instance, observed convulsions and ventricular tachycardia following unintended intravascular injection of bupivacaine during attempted peridural block. Aided by prompt resuscitation, electroshock alone sufficed to restore sinus rhythm. In any case, our patient showed no signs of superimposed toxicity from lidocaine, perhaps because diazepam had been given beforehand.

We do not recommend administering additional amide local anesthetic during florid convulsions. However, our case of gross bupivacaine overdosage, plus our experimental work with supraconvulsant doses of bupivacaine, suggest that lidocaine may be a useful adjunct in restoring sinus rhythm after convulsions have been terminated with a benzodiazepine. In any case, the backbone of the treatment of adverse reactions to local anesthetics remains early detection, and prompt support of ventilation and circulation.

ACKNOWLEDGMENTS

We thank Gerald Ostheimer, MD and Colette L. Lavoie at the Brigham and Women's Hospital for the bupivacaine determinations. Dr. Stephen Ripple participated in anesthetic care of the patient.

REFERENCES

1. Albright GA. Cardiac arrest following regional anesthesia with etidocaine or bupivacaine. Anesthesiology 1979;51:285–7.
2. Colley PA, Heavner JE. Blood levels of bupivacaine after injection into the scalp with and without epinephrine. Anesthesiology 1981;54:81–4.
3. Aps C, Reynolds F. The effect of concentration on vasoactivity of bupivacaine and lidocaine. Br J Anaesth 1976;48:1171–4.
4. Heinonen J, Takki S, Jarho L. Plasma lidocaine levels in patients treated with potential inducers of microsomal enzymes. Acta Anaesthesiol Scand 1970;14:89–95.
5. Bernhard CG, Bohm E. Local anesthetics as anticonvulsants: a study on experimental and clinical epilepsy. Stockholm: Almqvist and Wiksell, 1965.
6. Moore DC, Mather LE, Bridenbaugh LD. Arterial and venous plasma levels of bupivacaine following peripheral nerve blocks. Anesth Analg 1976;55:763–8.
7. Moore DC, Crawford RD, Scurlock JE. Severe hypoxia and acidosis following local anesthetic-induced convulsions. Anesthesiology 1980;53:259–60.
8. Block A, Covino BG. Effect of local anesthetic agents on cardiac conduction and contractility. Reg Anesth 1981;6:55–61.
9. de Jong RH, Heavner JE. Diazepam and lidocaine-induced cardiovascular changes. Anesthesiology 1973;39:633–8.
10. de Jong RH, Ronfeld RA, DeRosa RA. Cardiovascular effects of convulsant and supraconvulsant doses of amide local anesthetics. Anesth Analg 1982;61:3–9.
11. de Jong RH, Davis NL. Treating bupivacaine arrhythmias. Reg Anesth 1981;6:51–4.

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1982;61:65-6

Venous Air Embolism of Uncertain Etiology

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Venous air embolism is a well recognized complication of neurosurgery performed in the sitting position (1). Methods for detection and therapy for air entrainment have been discussed in the literature (2-5). We report a case of venous air embolism with unknown site of entry and discuss implications for monitoring and therapy.

Case Report

A 34-year-old, 75-kg man was scheduled for a posterior fossa craniotomy for excision of a recurrent clivus chordoma. Seven years previously partial excision of the tumor had been attempted, followed by treatment with both external radiation and chemotherapy. He had done well until the recurrence of symptoms approximately 1 year before this admission. He now had symptoms of bulbar palsy with difficulty in swallowing and speaking. History, review of systems, and physical examination were otherwise unremarkable.

The patient was premedicated with hydroxyzine, 150 mg orally. Upon arrival in the operating room, peripheral and internal jugular venous (CVP), and arterial (radial) catheters were placed. Monitors also included a Doppler ultrasonic probe placed over the precordium and an end-tidal CO_2 analyzer. Anesthesia was induced with intravenous thiopental, 1 g in divided doses, and intubation of the trachea was facilitated by the use of intravenous pancuronium bromide, 8 mg. A chest x-ray was taken to confirm placement of the central venous catheter in the right atrium. Anesthesia was maintained with 60% nitrous oxide 40% oxygen and divided doses of fentanyl. Ventilation was controlled with a tidal volume of 850 ml at a rate of 12 breaths per minute. The patient was raised slowly into the sitting position with the head in a three-point pinion headrest. All entry sites of the pinions were carefully covered with ointment. Vital signs remained stable. Following assumption of the sitting position maintanance of anesthesia was changed to 0.7% halothane in air and oxygen (F_{IO_2} 0.4). By 3½ hours following commencement of surgery, the tumor was fully exposed and examination revealed the tumor mass to be causing knuckling of the brainstem. At this time an air embolus was diagnosed by the Doppler ultrasonic detector and confirmed by a decrease in end-tidal CO_2. Approximately 30 ml of air was rapidly aspirated from the CVP catheter while the wound was flooded with saline. Vital signs remained stable, but air continued to be heard with the Doppler and was continuously aspirated from the central line. The wound was then covered with a layer of wet felt. No more air was heard on the Doppler and no air was aspirated from the CVP. After a few minutes the wound was carefully reexamined. Additionally, the CVP site, pinion sites, and the catheter and all stopcocks were carefully examined. No site of air entry was apparent. The wound was again exposed and air was immediately audible by Doppler and was again aspirated from the right atrium. This episode was accompanied by a decrease in mean arterial blood pressure of 30 torr (80 to 50) and a decrease in end-tidal CO_2 of 10 torr (25 to 15). Emergency closure was carried out. Signs of air embolism continued throughout closure, and even during dressing of the wound. These signs ceased only when the patient was returned to the supine position. A total of approximately 300 ml of air was aspirated from the central venous catheter. The patient was taken to the intensive care unit in stable condition with continuous ventilatory support. Postoperative recovery was uneventful.

Discussion

The incidence of venous air embolism in neurosurgical procedures performed in the sitting position and using the Doppler ultrasonic air detector as a monitor has been estimated to be approximately 25% (1). Such embolic phenomena are secondary to the presence of a negative gradient between surgically opened veins and the right side of the heart.

The case reported here is of interest because it represents an instance of confirmed venous air embolism without an evident site of entry. The surgeons were unable to stop the entrainment of air either by packing the wound or by rapid closure. One source for the air could have been the central venous line and its various stopcocks (6, 7). All these connections were examined (in and out of the patient) and found to be airtight. Another source for the air could have been the pin puncture sites. Wilkin and Albin (7) report three possible cases of such etiology. These sites were examined twice and found to be well occluded with ointment.

However, this case report is presented for another,

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Received from the Departments of Anesthesia and Surgery, Stanford University School of Medicine, Stanford University Medical Center, Stanford, California 94305. Accepted for publication September 10, 1981.

more important reason. Although it is of interest to consider the possible site of venous air embolism, the implication that this episode has for the on-going discussion of monitoring in neuroanesthesia is significant. It has been suggested that central venous catheterization may not be necessary in all neurosurgical procedures performed in the sitting position (2, 3). Munson (3) and Albin et al (4), however, argue that aspiration of the central venous catheter is an important maneuver in the diagnosis and treatment of venous air embolism (3, 4). Our patient sustained massive venous air embolism and severe alterations in cardiovascular status resulted. We were not able to stop the occurrence of embolism. We suggest that, without the early warning of the Doppler and specific treatment via aspiration of the central venous catheter of copious volumes of air, much more severe cardiopulmonary embarrassment would have ensued.

Thus, the argument put forth that the early detection of venous air embolism and prompt maneuvers by the surgeons obviates the need for right atrial catheterization is not supported by the events here described. Early detection and surgical awareness of the problem were ineffective in controlling this episode of venous air embolism. The use of the central venous catheter to counteract the continuing air embolism until the negative gradient was alleviated by position change was the crucial maneuver in this case. We recommend placement of central venous catheters in all posterior fossa craniotomies performed in the sitting position.

REFERENCES

1. Albin MS, Babinski M, Maroon JC, Jannetta PJ. Anaesthetic mangement of posterior fossa surgery in the sitting position. Acta Anaesthesiol Scand 1976;20:117–28.
2. Jackson PL. Intracardiac catheters unnecessary in neurosurgical anesthesia. Anesthesiology 1978;48:154.
3. Munson ES. Intracardiac catheters in neurosurgical anesthesia. Anesthesiology 1979;50:67–9.
4. Albin MS, Chang JL, Babinski M, Waterman P, Maivald P, Paulter S. Intracardiac catheters in neurosurgical anesthesia. Anesthesiology 1979;50:67–9.
5. Armstrong R, Peters JL, Cohen SL. Air embolism caused by fractured central venous catheters. Lancet 1977;1:954.
6. Ordway CB. Air embolus via CVP catheter without positive pressure. Ann Surg 1974;179:479–81.
7. Wilkin RH, Albin MS. An unusual entrance site of venous air embolism during operations in the sitting position. Surg Neurol 1977;7:71–2.

Intermittent Mandatory Ventilation and Weaning

Intermittent mandatory ventilation (IMV) was introduced to facilitate the weaning of patients from mechanical ventilation. The outcome of ventilator management in 116 patients who were treated in the first three months of 1975 was compared retrospectively with that of 135 patients who were treated in the first three months of 1976. All patients who were treated in 1975 received conventional (assisted or controlled) mechanical ventilation. In 1976, 77 patients (57%) were treated with the use of IMV, and 58 (43%) were treated with the use of conventional mechanical ventilation. Sixty-five patients who were treated in 1976 with the use of IMV were matched with patients who were treated in 1975 with the use of conventional ventilation, on the basis of age, sex, race, history of pulmonary disease, smoking history, diagnosis, service, and location of therapy. The average time spent on a ventilator by the IMV patients was 145 hours, whereas the matched control patients spent 142 hours. The length of hospitalization was 36 days for the IMV patients and 30 days for the control patients. These time periods were not significantly different and indicate that IMV did not reduce the length of ventilator management. *(Schachter EN, Tucker D, Beck GJ: Does intermittent mandatory ventilation accelerate weaning? JAMA 1981;246:1210–4)*

ANESTH ANALG
1982;61:67-8

Enflurane Seizures in Patients Taking Amitriptyline

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Even in patients without preexisting central nervous system disorders, enflurane has been reported to induce cerebral irritability and involuntary motor activity during its clinical use (1, 2). Similarly, tricyclic antidepressants in therapeutic doses and in overdoses are capable of producing both clinical and electroencephalographic evidence of seizure activity (3-5). As a result of this latter observation, it has been suggested that tricyclic antidepressants be used with caution in patients with lowered convulsive thresholds (6, 7). Therefore, although little is known about the effect of concomitantly administered medications on the seizure threshold of enflurane, the available data appear to indicate that the administration of enflurane to a patient taking tricyclic antidepressants might facilitate seizure activity. The following case reports suggest that such an interaction between enflurane and tricyclic antidepressants does exist.

Case Reports

Case 1

A 42-year-old woman with mandibular atrophy was scheduled for placement of a mandibular autologous rib graft. Preoperative physical and laboratory evaluations were unremarkable except for a history of depression for which she took amitriptyline, 100 mg, each day.

Fifty minutes after receiving oral diazepam, 5 mg, the patient arrived in the operating room in a comfortable, alert state. Anesthesia was induced with thiopental, 250 mg; succinylcholine, 80 mg, was administered to facilitate placement of a nasotracheal tube. Anesthesia was maintained with fentanyl, 1.0% to 1.5% enflurane, and 60% nitrous oxide in oxygen. Respirations were controlled by use of a volume ventilator, and arterial blood gas tensions were intermittently measured. Approximately 3 hours after induction of anesthesia, clonic movements of the patient's right hand and forearm occurred. At this time, the patient was receiving 1% enflurane and 60% nitrous oxide in oxygen; blood pressure, pulse rate, and temperature remained unchanged; the serum electrolyte levels were within the normal range; arterial blood gases were pH 7.44, P_{O_2} 135 torr, and P_{CO_2} 34 torr. Because the focal seizure continued unabated, the patient was allowed to initiate spontaneous respirations in an attempt to increase the arterial carbon dioxide tension. Once the patient had resumed spontaneous respirations, the arterial blood gases were pH 7.35, P_{O_2} 143 torr, and P_{CO_2} 46 torr. As this change in ventilation did not affect the involuntary movements, enflurane was discontinued and 1% halothane was administered. Approximately 1 minute thereafter, the movements decreased in frequency and amplitude and, subsequently, disappeared. After surgery the patient awoke quickly and, while in the recovery room, she had a neurologic examination, the findings of which were normal. An electroencephalogram (EEG) was performed on the 2nd postoperative day and was within normal limits; her subsequent clinical course was uneventful.

Case 2

A 39-year-old man was scheduled for excision of a left parotid mass under general anesthesia. The patient had been in good health except for a history of depression for which he took amitriptyline, 150 mg, each day. Preoperative physical and laboratory evaluations were unremarkable except for the presence of the parotid mass.

Eighty minutes after receiving oral pentobarbital, 100 mg, the patient received thiopental, 300 mg, to induce anesthesia. Then, succinylcholine, 100 mg, was administered intravenously to facilitate the passage of an endotracheal tube. Anesthesia was maintained with 1.0% to 2.0% enflurane, 65% nitrous oxide in oxygen, and intermittent doses of fentanyl. Once muscle tone returned, spontaneous breathing with an occasional assisted breath was instituted. Approximately 1 hour later, intermittent clonic movements of the right leg and arm were noted. At this time, the patient was receiving 1.5% enflurane and 65% nitrous oxide in oxygen; blood pressure was 130/90 torr; pulse rate was 90 beats per minute; temperature was 37 C; serum electrolyte levels were normal; and arterial blood gases were pH 7.37, P_{O_2} 125 torr, and P_{CO_2} 45 torr. Because the involuntary movements continued, enflurane was discontinued and halothane was administered. Approximately 2 minutes after the anesthetics were changed, the involuntary movements disappeared, and no further movements were noted during the remaining 3 hours of anesthesia. After surgery the patient awoke quickly and had an uneventful postoperative recovery.

Discussion

Early in its clinical trials, enflurane was reported to induce in anesthetized patients electroencephalographic patterns resembling those seen during sei-

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Received from the Department of Anesthesiology, University of North Carolina, Chapel Hill, North Carolina 27514. Accepted for publication September 14, 1981.
Reprint requests to Dr. Sprague.

zures (1, 2). Often, these abnormal electroencephalographic patterns were associated with concurrent motor activity (2, 3). The incidence of enflurane-induced involuntary motor activity has been reported to increase both as the depth of enflurane anesthesia is increased and as the arterial carbon dioxide tension is reduced (1, 2, 8).

Although high concentrations of enflurane and low carbon dioxide tensions are well established inducers of abnormal EEG activity, the effects of concomitantly administered medications on the seizure threshold of enflurane have been addressed in only a few studies. Neigh et al (2) found in man that the addition of 60% nitrous oxide to 1.5% to 3.4% enflurane at carbon dioxide tensions of 21 to 32 torr did not alter the predominant EEG pattern. In cats, Furgang and Sohn (9) observed that, during light enflurane anesthesia, intravenous thiopental could exacerbate EEG signs of seizure activity and, during deep enflurane anesthesia, intravenous thiopental could suppress spike activity. Darimont and Jenkins (10) also have shown in cats that methohexital, diazepam, and ketamine enhance established enflurane-induced EEG seizure activity. In addition, diazepam appeared to lower the seizure threshold to an enflurane challenge, an effect that was most marked when the carbon dioxide tension was lowered.

The effects of tricyclic antidepressants on cerebral irritability during enflurane anesthesia are unknown. However, numerous reports (3–7) have documented the potential for tricyclic antidepressants to lower the seizure threshold and to induce seizure activity in nonanesthetized patients with and without a history of a central nervous system disorder. Although the clinical importance of these effects are not readily predictable, it has been suggested that tricyclic antidepressants be used with caution in patients whose convulsive threshold might be lowered and that, when used, an anticonvulsant drug be administered simultaneously (6, 7).

In the patients described here, we believe that amitriptyline, by decreasing the seizure threshold, could have enhanced the development of the observed motor activity during enflurane anesthesia. Besides the above experimental data, a number of clinical observations during the development of seizures in our patients led to this conclusion. In both patients, low concentrations of enflurane (1.0% and 1.5%) were being administered when the seizure developed, and relatively low concentrations (1.0% to 2.0%) were used before the seizure. Because the depth of anesthesia due to enflurane is considered the most important factor influencing the development of an enflurane seizure (2), development of a seizure at low concentrations of enflurane suggests a lowering of the seizure threshold.

Also, in both patients, arterial carbon dioxide tensions before and at the time of the abnormal motor activity were near normal. In the first patient, the P_{CO_2} was slightly reduced before and at the time of the seizure; however, the P_{CO_2} was not reduced to levels that would be expected to enhance seizure activity at low concentrations of enflurane. In addition, in this patient the elevation of the P_{CO_2} to normal levels after the seizure developed did not influence the motor activity. In the second patient, seizure activity developed during spontaneous respiration when carbon dioxide tensions were greater than 40 torr. Because levels of P_{CO_2} of 45 torr and greater have been shown to reduce cerebral irritability (2), a role for P_{CO_2} in the development of seizure activity in this patient is unlikely.

In summary, it appears likely that the enflurane-induced seizure activity observed in our two patients could have been enhanced by the presence of amitriptyline. Therefore, although the cerebral irritability that occurs with enflurane does not seem to pose any major clinical problem, it may be advisable to avoid the use of enflurane in patients requiring tricyclic antidepressants; this may be especially important when the patient has a history of seizures or when hyperventilation or high concentrations of enflurane are a desired part of the anesthetic technique.

REFERENCES

1. Linde HW, Lamb VE, Quimby CW, Homi J, Eckenhoff JE. The search for better anesthetic agents: clinical investigation of Ethrane. Anesthesiology 1970;32:555–9.
2. Neigh JL, Garman JK, Harp JR. The electroencephalographic pattern during anesthesia with Ethrane. Anesthesiology 1971;35:482–7.
3. Kiloh LG, Davison K, Osselton JW. An electroencephalographic study of the analeptic effects of imipramine. Electroencephalogr Clin Neurophysiol 1961;13:216–23.
4. Davison K. EEG activation after intravenous amitriptyline. Electroencephalogr Clin Neurophysiol 1965;19:298–300.
5. Betts TA, Kalra PL, Cooper R, Jeavons PM. Epileptic fits as a probable side-effect of amitriptyline. Lancet 1968;1:390–2.
6. Dallos V, Heathfield K. Iatrogenic epilepsy due to antidepressant drugs. Br Med J 1969;4:80–2.
7. Brown D, Winsberg BG, Bialer I, Press M. Imipramine therapy and seizures: three children for hyperactive behavior disorders. Am J Psychiatry 1973;130:210–2.
8. Lebowitz MH, Blitt CD, Dillon JB. Enflurane-induced central nervous system excitation and its relation to carbon dioxide tension. Anesth Analg 1972;51:355–63.
9. Furgang FA, Sohn JJ. The effect of thiopentone on enflurane-induced cortical seizures. Br J Anaesth 1977;49:127–32.
10. Darimont PC, Jenkins LC. The influence of intravenous anaesthetics on enflurane-induced central nervous system seizure activity. Can Anaesth Soc J 1977;24:42–56.

letters
TO THE EDITOR

Positioning the Ultrasonic Doppler Flow Detector Probe in Small Children

To the Editor:

We use an ultrasonic Doppler flow detector as an aid in monitoring the end point during measurement of systolic blood pressure at the wrist (radial artery) or antecubital fossa (brachial artery) with the sphygmomanometer in premature infants, term infants, and small children.

The major problem encountered, particularly in very small infants, is the tendency of the coupling surface of the probe to change position when the cable is twisted in any way during repositioning of the baby's arm. This results in diminution or loss of flow detection.

In order to fix the position of the probe somewhat independent of the cable, we have cut the cable 2.5 cm from the distal end of the probe and reconnected it to a 5-cm piece of flexible cable (Figs 1 and 2). This does not seem to interfere with the efficiency of the device.

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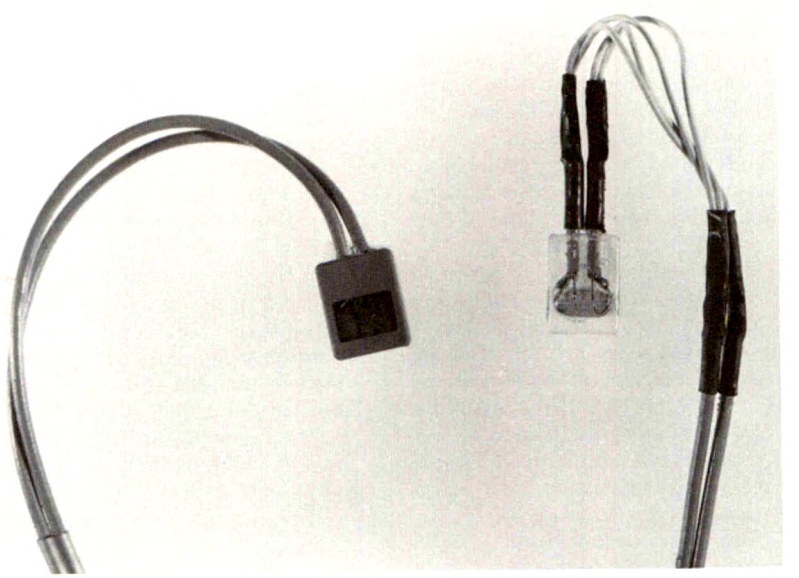


FIG 1. Left, original probe and cable of ultrasonic Doppler flow detector device. Hook shape of cable gives an idea of its stiffness. Right, similar probe joined to original cable by very flexible shielded wires. This modification allows probe to assume and maintain positions independent of lead cable.

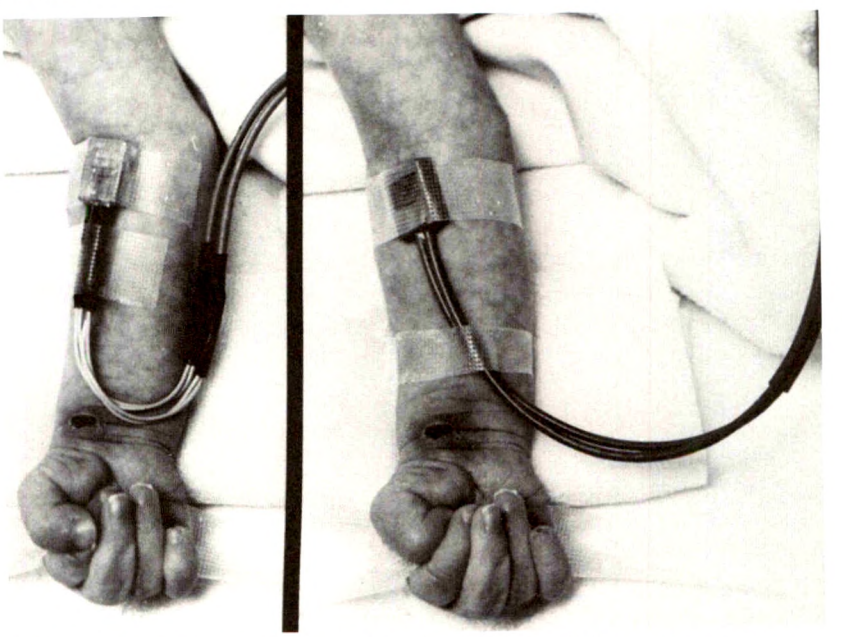


FIG 2. Hand of neonate who previously had an arterial line inserted into radial artery by cutdown. Left, ultrasonic Doppler probe with modified cable is positioned well on antecubital fossa without twisting. Right, similar probe with original cable. Inflexible cable tends to twist probe's coupling surface from its original position, resulting in diminution or loss of flow detection.

Respiratory Depression after Intrathecal Morphine

To the Editor:

In a recent editorial, Bromage (1) suggested that delayed respiratory depression after intrathecal morphine may be due to poor lipid solubility and slow transfer of the drug into the fourth ventricle. This suggestion has been supported by Paulus et al (2), who reported a case of neurologic and respiratory depression after accidental intrathecal administration of morphine, 20 mg.

It has been recently recommended that intrathecal morphine in doses up to 0.02 mg/kg should not be administered for at least 4 hours after any systemic injection of opioid analgesic (3). We report here two cases of delayed respiratory depression following intrathecal morphine which may have been due to parenteral opioid analgesic administration.

The first patient was a 74-kg woman, aged 73 years, who underwent resection of an abdominal aortic aneurysm. Anesthesia was with methohexital, succinylcholine, N_2O/O_2, and enflurane. Pancuronium was used for muscle relaxation. Intrathecal morphine, 3 mg, in 10 ml of 5% dextrose (without preservative) was injected at L2-3 after induction of anesthesia.

After a 5-hour operation, the patient was awake and, following 45 minutes of spontaneous respiration, had a Pa_{CO_2} of 42 torr and a Pa_{O_2} of 110 torr. She was extubated and sent to the intensive care unit. On arrival in the intensive care unit, the patient was given piritramide, 10 mg IM, because of restlessness which was misinterpreted as pain. (Piritramide is a synthetic opioid with a duration of action similar to that of morphine). Half an hour later, the patient's respiratory rate decreased to 6 breaths per minute with Pa_{CO_2} of 60 torr. She responded to naloxone, 0.2 mg IV, with a respiratory rate of 16 breaths per minute and a Pa_{CO_2} of 40 torr. Thirty minutes after the administration of naloxone, slow respiration developed again and she was given a second dose of naloxone, 0.2 mg. Respiration then improved but remained inadequate with a Pa_{CO_2} of 55 torr. She was intubated and ventilated until the following morning, when she was extubated without further complications.

The second patient was a 78-kg man, aged 82 years, anesthetized using a similar technique for resection of an abdominal aortic anaerusym. At the end of a 6-hour operation, the patient was transferred to the intensive care unit with the endotracheal tube in situ and, as the body temperature was 33.5 C, he was ventilated with a Servo ventilator with the trigger set at −10 torr. He continued to trigger the ventilator satisfactorally during the night, and 21 hours after surgery piritramide, 10 mg, was given intramuscularly for sedation according to the surgeon's protocol. Within 40 minutes, the patient failed to trigger the ventilator, became apneic and remained so for 30 hours. When naloxone, 0.2 mg, was administered intravenously the patient began breathing spontaneously with a respiratory frequency of 16 breaths per minute and Pa_{CO_2} of 35 torr. The endotracheal tube was removed and there was no recurrence of respiratory depression.

These two cases serve to illustrate the possible dangerous potentiation of opioid-induced respiratory depression which may occur with the concomitant use of intrathecal morphine and parenteral opioid administration.

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REFERENCES

1. Bromage PR. The price of intraspinal narcotic analgesia: basic constraints. Anesth Analg 1981;60:461–3.
2. Paulus DA, Paul WL, Munson ES. Neurologic depression after intrathecal morphine. Anesthesiology 1981;54:517–8.
3. Samii K, Chavin M, Viars P. Postoperative spinal analgesia with morphine. Br J Anaesth 1981;53:817–20.

book REVIEWS

Clinical Aspects of Oxygen: International Anesthesiology Clinics, Volume 19, Number 3, Fall 1981, edited by J. B. Brodsky, Boston, Little, Brown and Co., 1981, 267 pp, $40.00/yr.

This newest volume in the highly regarded *International Anesthesiology Clinics* series is designed to fill an important void. The last major, multiauthor work dealing with oxygen was the 1972 symposium published in *Anesthesiology*.

In the intervening 9 years, both clinical anesthesiology and basic research have made great strides, particularly in the areas of cardiorespiratory physiology and pathology and in their translation into rational clinical practice.

The present volume comes close to accomplishing its purpose although it, regretfully, falls short in several important areas. It suffers from the generic weakness of multiauthor efforts. The chapters are uneven in quality, orientation, and usefulness. They all reveal great scholarship and a profound understanding of complex phenomena. Unfortunately, some are too technical for the average practitioner, and although most of the chapters will have an effect in modifying clinical understanding, few are likely to modify clinical behavior.

The primary usefulness of this volume will be for residents reading for board examinations, faculty preparing lectures, and clinicians who have great intellectual curiosity. For these, the volume will be invaluable both directly and through the extensive bibliography appended to most chapters.

The 11 essays deal with various aspects of oxygen from "Oxygen: A Drug" by Brodsky to "Hemodilution and Oxygenation" by Priebe. The intervening essays tackle problems such as "Oxygen and Intracellular Metabolism" by Cohen, "Oxygen Transport" by Clemmer, "The Oxyhemoglobin Dissociation Curve" by Sladen, and "Oxygen Stores" by Stirt and Sullivan. Two chapters by Kafer and Sugioka and by Klineberg and Bagshaw deal with hypoxemia. Two chapters by Raffin and by Miller and Winter deal with oxygen toxicity, and Kennedy and Wilson authored a chapter titled "Oxygen Measurements."

All the chapters are of interest. The two chapters on oxygen toxicity are informative and useful. Miller and Winter have the ability to focus on essentials. Kennedy and Wilson give a fine review on O_2 measurement both in the research laboratory and at the bedside. Their chapter, although somewhat repetitious, is useful and interesting. Priebe writes well and presents important information. Cohen has the ability to present a complicated matter clearly and succinctly.

The remaining chapters have clinical usefulness, but the clinically relevant information is difficult to find among the technical minutiae which tend to overwhelm all but the very sophisticated reader. These chapters are written by experts for experts and contain all the details that delight the scholar but that may exasperate the practitioner.

To some extent, this is a reflection on the liberality of the editor who gave the contributors too much individual freedom and who did not insist that the clinically important aspects of this significant area be emphasized for the practitioner.

It is a great pity that such a valuable contribution will be enjoyed by relatively few and will be found practically useful by even fewer.

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Perchance to Dream, by R. C. Brown, Chicago, Nelson-Hall Publishers, 1981, 86 pp, $10.95.

Note: Events conspired to cause this book to arrive on the Book Review Editor's desk just prior to an elective femoral osteotomy on his daughter. She kindly agreed to read the book prior to her surgical experience and write a review from the standpoint of an average patient. Other than copy-editing, it is presented as she wrote it.

Surgery can be a frightening prospect for any patient, and the fear is often largely generated by ignorance. The surgeon is usually informative about his treatment and has described what he plans to do several times, but there are other aspects of surgery that are sources of anxiety, as well, particularly anesthesia. Information about this subject is difficult for the patient to find on his own and even more difficult to understand. In response to this need, an anesthesiologist has written a patient's guide to anesthesia, *Perchance to Dream*.

This book attempts to give its readers an idea of what happens to the body and the nervous system during anesthesia and surgery. It reviews the different types of anesthetics and the effects on the patient, as well as what the anesthesiologist must do throughout the operation to ensure the patient's insensitivity and safety. It also

explains some of the problems that can complicate surgery and anesthesia.

I recently underwent major surgery and I received a copy of this book before the operation. It was not the first time I'd had surgery, but it's amazing how quickly and completely one forgets what the experience is like once it's over and I don't mind admitting that I was more than a little afraid. I simply didn't know what to expect. I hoped that by reading this book my fears would be minimized, but I was disappointed.

I think part of the problem is the disparity between the knowledge of the doctor and the patient on this subject. Dr. Brown's many years of training seem to have frustrated him in his attempt to translate complex processes into simple concepts that a patient with no medical background can understand. In general, the author ranges from condescending to confusing in his presentation of the history and function of anesthesiology. Many of his analogies are oversimplified, and in some cases they are not effective in illustrating the point. At times the initial description of a process or an effect is too technical for the layman's understanding, and when this is coupled with an oversimplified analogy, the reader is baffled by the information.

There is also a noticeable disparity between the emotional attitude of the doctor and that of the patient. For the former, surgery is routine and a common part of every work day, whereas for the patient the very idea holds countless terrors, both real and imagined. I feel that Dr. Brown ignores the emotional needs of his intended audience. An example of this is his insistant use of the word "knife" as opposed to the more technical but infinitely more comforting term "scalpel." I found that "knife" elicited an unexpected emotional response within me and I was intimidated by its use.

Similarly, the chapter on the possible complications of anesthesia was intimidating. This is the last chapter of the book, and it is essentially a list of cases in which the patient died or suffered irrevocable damage as a result of a slight miscalculation on the part of the anesthesiologist or of an unforeseen reaction in the patient to one or more of the drugs used during the operation. Although I recognize the importance of informing a patient of these potential problems, I believe that it can be done without leaving the person in agonizing doubt about his safety. I mentioned above that I was apprehensive about my impending surgery, but after finishing this book I was terrified and left instructions as to how to distribute my belongings should I die during surgery, which I was convinced would happen.

The night before the operation, the anesthesiologist visited me to say a few words and to answer any questions I might have. At least, that's what I was told. As it happened, there were indeed some points about which I was confused but when I asked for clarification, I found that the doctor was totally unprepared for such a request. My impression was that I had overstepped my bounds somehow, and I (finally) fell asleep knowing no more than I had earlier. I don't fault the doctor for this, though, because I realize that most anesthesiologists are unaccustomed to questions at all because most patients scarcely know what to ask. Without background information the facts are quite alarming to the patient but the doctor usually doesn't have the time to hold a seminar to explain what will happen in the operating room.

I wish that *Perchance to Dream* were the educational work that is needed for those facing surgery, but it simply isn't. It seems to be less a patient's guide than it is a plea for some recognition of the anesthesiologist's difficult job and an apology for malpractice, at the expense of the audience it was intended to reach.

Gillian Didier
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Pain: Origin and Treatment, by B. H. Gorsky, Garden City, NY, Medical Examination Publishing Co., Inc., 1981, 123 pp, $16.50 ($9.50 paperback).

This short monograph is both delightful and surprising. In 99 pages of text, Gorsky presents a concise overview of pain management from the perspective of many medical disciplines: surgery, anesthesiology, and psychology. It is not a detailed account of the management of specific clinical situations, nor is it a cookbook of techniques, but rather it serves best as a general introduction to the subject.

Gorsky obviously has made great effort to be both concise and yet informative to readers with many levels of training and experience. The narrative is such that much could easily be understood by the interested lay person, but still there is sufficient material for the practitioner with a beginning interest in the treatment of patients with chronic pain. Furthermore, he does this with both humor and clarity.

Chapters in the text are devoted to the physiology and perception of pain, the pharmacology of analgesics, surgical and other modalities used in pain relief, and the psychological aspects of chronic pain. Overall, more attention is given to the psychological implications of chronic pain than to any other.

This is a good little introductory text on chronic pain management. Although this book appears at a time when there seem to be almost too many from which to choose, it is, however, well worth reading.

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BOOK NOTE

Respiratory Physiology, Fourth Edition, by N. B. Slonim and L. H. Hamilton, St. Louis, C. V. Mosby Co., 1981, 301 pp, $17.95.

This is the 5-year update on *Respiratory Physiology* aimed at the medical student level. It covers the subject thoroughly without excessive detail, and contains a useful appendix containing symbols, conversion tables, formulas, nomograms, and other such useful information.

BOOKS RECEIVED

Basic Pharmacology in Medicine, Second Edition, by J. R. DiPalma, New York, McGraw-Hill Book Co, 1981, 517 pp, $25.00.

Coagulation: The Essentials, by D. P. Fischbach and R. P. Fogdall, Baltimore, Williams & Wilkins Co, 1981, 252 pp, $19.00.

Anesthesia: Volumes 1 and 2, edited by R. D. Miller, New York, Churchill Livingstone, Inc, 1981, 1535 pp, $98.00/set.

Problems in Anesthesia: A Case Study Approach, by M. B. Ravin, Boston, Little, Brown and Co, 1981, 259 pp, $14.95.

Drug-Nutrient Interactions, Volume 1, by D. A. Roe, New York, 1981, 88 pp, $70.00/yr.

Profile of an Anaphylactic Reaction

A 28-year-old woman undergoing elective total hip replacement experienced an anaphylactic reaction to succinylcholine. Hemodynamics, plasma histamine, and catecholamines were measured. Immediately after the administration of succinylcholine and concurrent with the appearance of flushing, a substantial increase in cardiac output and stroke volume occurred. Although systemic vascular resistance fell precipitously from 1000 to 602 dyn·sec·cm^{-5}, arterial blood pressure declined slightly from 105/60 to 100/50 mm Hg. Massive release of histamine and catecholamines was indicated by large increases in their respective blood levels. Three minutes after administration of succinylcholine, heart rate increased dramatically to 147 beats per minute, but cardiac index and systemic vascular resistance remained unchanged. Stroke volume decreased sharply. Norepinephrine levels rose to 2625 pg/ml, but epinephrine levels decreased from 1961 pg/ml at 1 minute to 1032 pg/ml at 3 minutes. Histamine levels remained elevated. Plasma histamine and epinephrine were markedly elevated despite only a modest decrease in blood pressure. It is likely that epinephrine release was a consequence of histamine's action on the adrenal glands, although a reflex action through the baroreceptors or by central nervous stimulation is possible. The correlation between endogenous norepinephrine levels and heart rate suggests that the tachycardia was a reflection of massive sympathetic activation rather than a direct chronotropic effect of histamine. *(Moss J, Fahmy NR, Sunder N, Beaven MA: Hormonal and hemodynamic profile of an anaphylactic reaction in man. Circulation 1981;63:210–3)*

A Guide for Authors

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Nicholas M. Greene, M.D.
Editor in Chief
Anesthesia and Analgesia
Yale University School of Medicine
333 Cedar Street
New Haven, Connecticut 06510

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Illustrations and other materials taken from other sources must be properly credited and assurance provided that permission for reproduction has been obtained from the copyright owner and author.

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Manuscripts must be prepared and submitted in the manner described in "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" as described in Annals of Internal Medicine 1979; 90: 95–9, and Lancet 1979; 1: 428–30.

Type manuscripts on white bond paper, 20.3 by 26.7 cm or 21.6 by 27.9 cm (8 by 10½ in or 8½ by 11 in) or ISO A4 (212 by 297 mm) with margins of at least 2.5 cm (1 in). Use double spacing throughout, including title page, abstract, text, acknowledgments, references, tables, and legends for illustrations.

Begin each of the following sections on separate pages: title page, abstract and key words, text, acknowledgments, references, tables (each table, complete with title and footnotes, on a separate page), and legends. Number pages consecutively, beginning with the title page. Type the page number in the upper right-hand corner of each page.

Illustrations must be good quality, unmounted glossy prints, usually 12.7 by 17.3 cm (5 by 7 in), but no larger than 20.3 by 25.4 cm (8 by 10 in).

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Text. The text of observational and experimental articles is usually—but not necessarily—divided into sections with the headings Introduction, Methods, Results, and Discussion. Long articles may need subheadings within some sections to clarify their content, especially the Results and Discussion sections. Case reports and reviews do not require the above sections.

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Include numbers of observations and the statistical significance of the findings when appropriate. Detailed statistical analyses, mathematical derivations, and the like may sometimes be suitably presented in the form of one or more appendixes.

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Discussion. Emphasize the new and important aspects of the study and *conclusions* that follow from them. Do not repeat in detail data given in the Results section. Include in the Discussion the implications of the findings and their limitations and relate the observations to other relevant studies. Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not completely supported by your data. Avoid claiming priority and alluding to work that has not been completed. State new hypotheses when warranted, but clearly label them as such. Recommendations, when appropriate, may be included.

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Journal

1. Standard Journal Article (List all authors when six or less; when seven or more, list only first three and add et al)

   Soter NA, Wasserman SI, Austen KF. Cold urticaria: release into the circulation of histamine and eosinophil chemotactic factor of anaphylaxis during cold challenge. N Engl J Med 1976;294:687–90.

2. Corporate Author

   The Committee on Enzymes of the Scandinavian Society for Clinical Chemistry and Clinical Physiology. Recommended method for the determination of gamma-glutamyltransferase in blood. Scand J Clin Lab Invest 1976;36:119–25.

   Anonymous. Epidemiology for primary health care. Int J Epidemiol 1976;5:224–5.

Books and Other Monographs

3. Personal Author(s)

   Osler AG. Complement: mechanisms and functions. Englewood Cliffs: Prentice-Hall, 1976.

4. Corporate Author

   American Medical Association Department of Drugs. AMA drug evaluations. 3rd ed. Littleton: Publishing Sciences Group, 1977.

5. Editor, Compiler, Chairman as Author

   Rhodes AJ, Van Rooyen CE, comps. Textbook of virology: for students and practitioners of medicine and the other health sciences. 5th ed. Baltimore: Williams & Wilkins, 1968.

6. Chapter in Book

   Weinstein L, Swartz MN. Pathogenic properties of invading microorganisms. In: Sodeman WA Jr, Sodeman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: WB Saunders, 1974:457–72.

7. Agency Publication

   National Center for Health Statistics. Acute conditions: incidence and associated disability, United States July 1968–June 1969. Rockville, Md.: National Center for Health Statistics, 1972. (Vital and health statistics. Series 10: Data from the National Health Survey, no. 69) (DHEW publication no. (HSM)72–1036).

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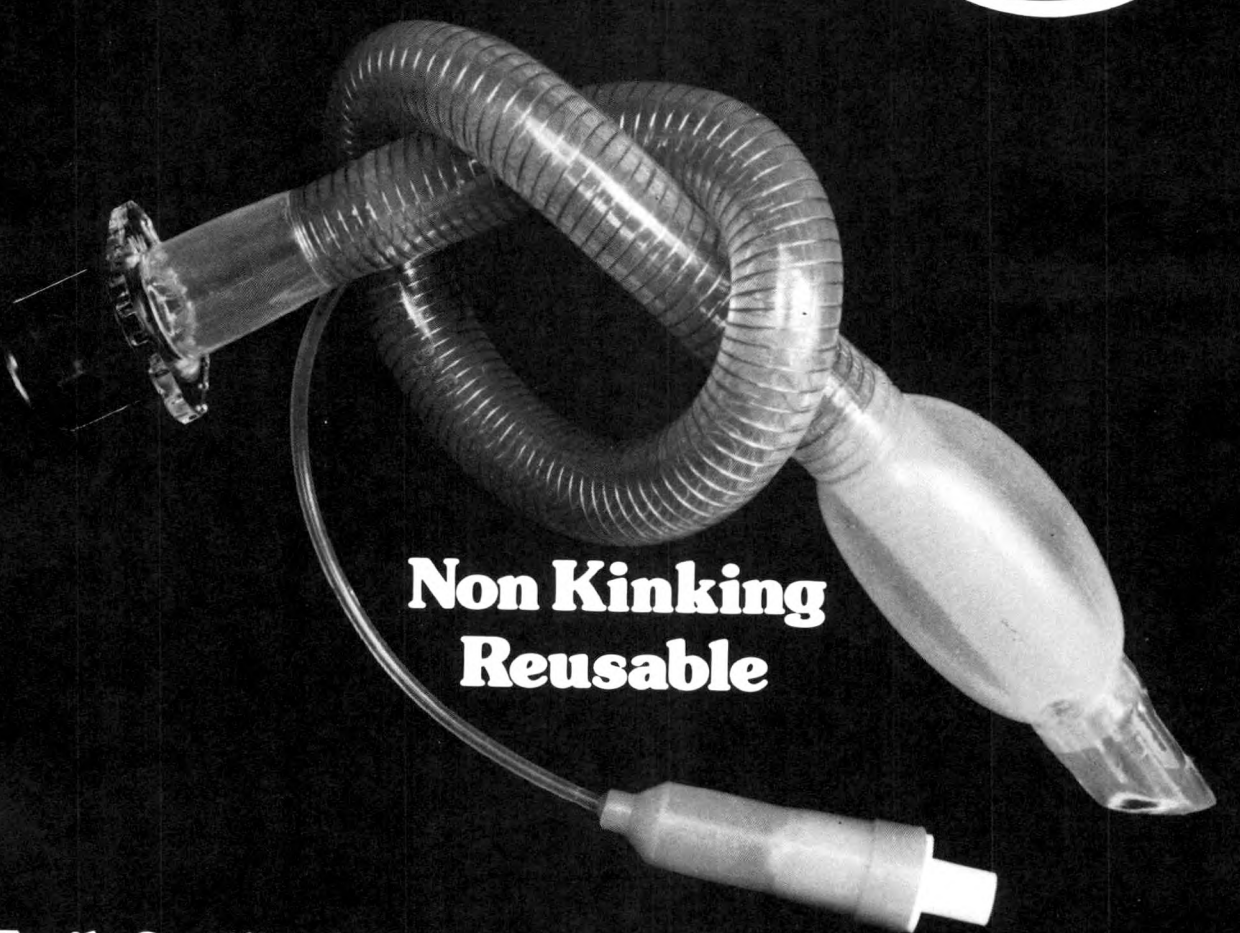
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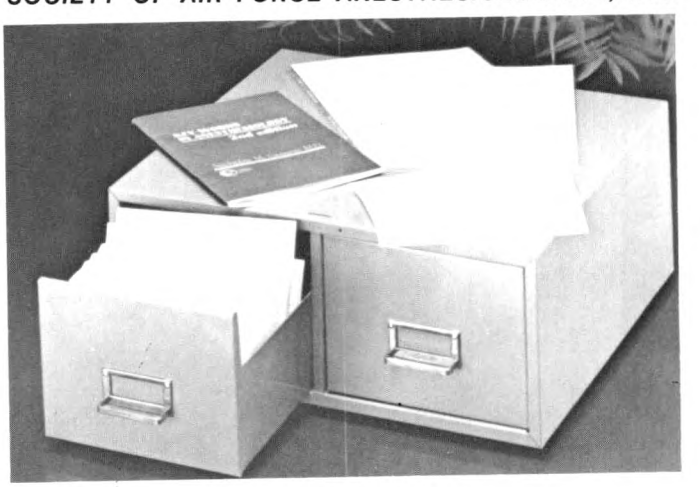
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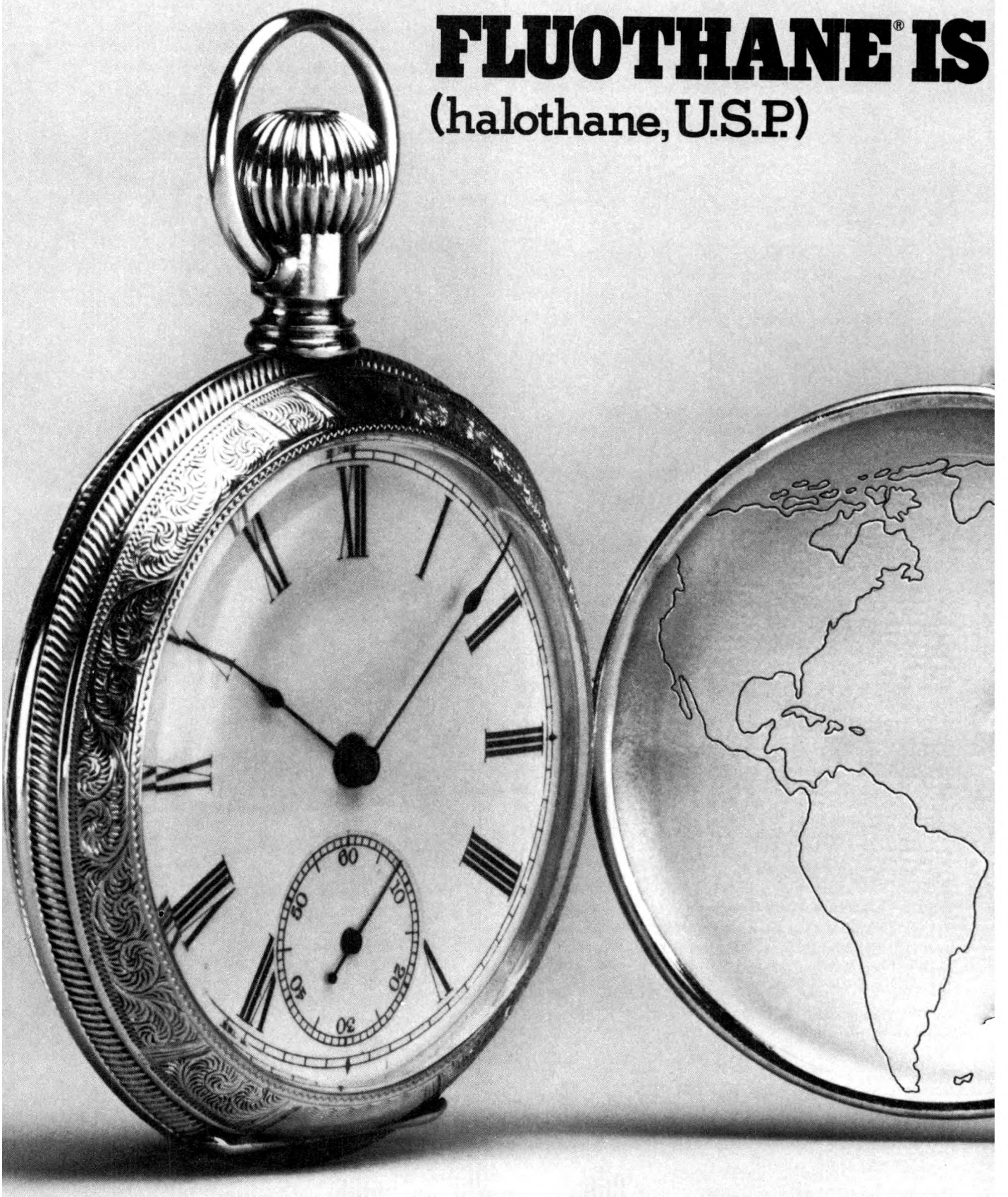
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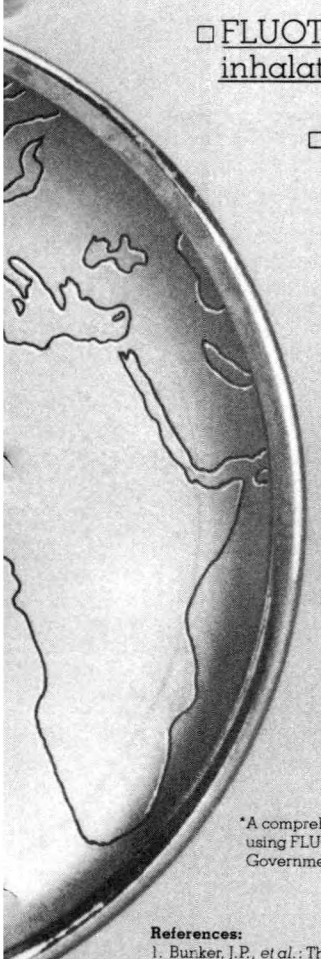
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*A comprehensive retrospective analysis covering 856,000 general anesthesias—nearly one-third using FLUOTHANE. Bunker, J.P., *et al.*: The National Halothane Study. Washington, D.C., Government Printing Office, 1969.

References:

1. Bunker, J.P., *et al.*: The National Halothane Study. Washington, D.C., Government Printing Office, 1969.
2. Brown, B.R., Sipes, I.G.: Biochem. Pharmacol. 26:2091-2094, 1977.
3. Steward, D.J.: Anesthesiology 43:268-276 (Aug.) 1975.
4. Proceedings, Virginia Society of Anesthesiologists, April 20-22, 1979, Richmond, VA.

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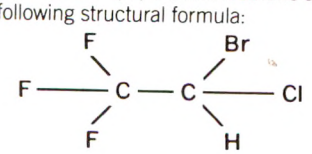
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FLUOTHANE does not decompose in contact with warm soda lime. When moisture is present, the vapor attacks aluminum, brass, and lead, but not copper. Rubber, some plastics, and similar materials are soluble in FLUOTHANE; such materials will deteriorate rapidly in contact with FLUOTHANE vapor or liquid. Stability of FLUOTHANE is maintained by the addition of 0.01 per cent thymol (w/w), up to 0.00025% ammonia (w/w), and storage is in amber colored bottles.

FLUOTHANE should not be kept indefinitely in vaporizer bottles not specifically designed for its use. Thymol does not volatilize along with FLUOTHANE, and therefore accumulates in the vaporizer, and may, in time, impart a yellow color to the remaining liquid or to wicks in vaporizers. The development of such discoloration may be used as an indicator that the vaporizer should be drained and cleaned, and the discolored FLUOTHANE (halothane, U.S.P.) discarded. Accumulation of thymol may be removed by washing with diethyl ether. After cleaning a wick or vaporizer, make certain all diethyl ether has been removed before reusing the equipment to avoid introducing ether into the system.

Actions. FLUOTHANE is an inhalation anesthetic. Induction and recovery are rapid and depth of anesthesia can be rapidly altered. FLUOTHANE progressively depresses respiration. There may be tachypnea with reduced tidal volume and alveolar ventilation. FLUOTHANE is not an irritant to the respiratory tract, and no increase in salivary or bronchial secretions ordinarily occurs. Pharyngeal and laryngeal reflexes are rapidly obtunded. It causes bronchodilation. Hypoxia, acidosis, or apnea may develop during deep anesthesia.

FLUOTHANE reduces the blood pressure, and frequently decreases the pulse rate. The greater the concentration of the drug, the more evident these changes become. Atropine may reverse the bradycardia. FLUOTHANE does not cause the release of catecholamines from adrenergic stores. FLUOTHANE also causes dilation of the vessels of the skin and skeletal muscles.

Cardiac arrhythmias may occur during FLUOTHANE anesthesia. These include nodal rhythm, AV dissociation, ventricular extrasystoles and asystole. FLUOTHANE sensitizes the myocardial conduction system to the action of epinephrine and norepinephrine, and the combination may cause serious cardiac arrhythmias. FLUOTHANE increases cerebral spinal fluid pressure. FLUOTHANE produces moderate muscular relaxation. Muscle relaxants are used as adjuncts in order to maintain lighter levels of anesthesia. FLUOTHANE augments the action of nondepolarizing relaxants and ganglionic blocking agents. FLUOTHANE is a potent uterine relaxant.

Indications. FLUOTHANE (halothane, U.S.P.) is indicated for the induction and maintenance of general anesthesia.

Contraindications. FLUOTHANE is not recommended for obstetrical anesthesia except when uterine relaxation is required.

Warnings. When previous exposure to FLUOTHANE was followed by unexplained jaundice, consideration should be given to the use of other agents.

FLUOTHANE should be used in vaporizers that permit a reasonable approximation of output, and preferably of the calibrated type. The vaporizer should be placed out of circuit in closed circuit rebreathing systems; otherwise overdosage is difficult to avoid. The patient should be closely observed for signs of overdosage, *i.e.*, depression of blood pressure, pulse rate, and ventilation, particularly during assisted or controlled ventilation.

Usage in Pregnancy. Safe use of FLUOTHANE has not been established with respect to possible adverse effects upon fetal development. Therefore, FLUOTHANE should not be used in women where pregnancy is possible and particularly during early pregnancy, unless, in the judgment of the physician, the potential benefits outweigh the unknown hazards to the fetus.

Precautions. The uterine relaxation obtained with FLUOTHANE, unless carefully controlled, may fail to respond to ergot derivatives and oxytocic posterior pituitary extract.

FLUOTHANE increases cerebrospinal fluid pressure. Therefore, in patients with markedly raised intracranial pressure, if FLUOTHANE is indicated, administration should be preceded by measures ordinarily used to reduce cerebrospinal fluid pressure. Ventilation should be carefully assessed, and it may be necessary to assist or control ventilation to insure adequate oxygenation and carbon dioxide removal.

Epinephrine or norepinephrine should be employed cautiously, if at all, during FLUOTHANE (halothane, U.S.P.) anesthesia since their simultaneous use may induce ventricular tachycardia or fibrillation.

Nondepolarizing relaxants and ganglionic blocking agents should be administered cautiously, since their actions are augmented by FLUOTHANE.

It has been reported that in genetically susceptible individuals, the use of general anesthetics and the muscle relaxant, succinylcholine, may trigger a syndrome known as malignant hyperthermic crisis. Monitoring temperature during surgery will aid in early recognition of this syndrome. Dantrolene sodium and supportive measures are generally indicated in the management of malignant hyperthermia.

Adverse Reactions. The following adverse reactions have been reported: mild, moderate and severe hepatic dysfunction (including hepatic necrosis), cardiac arrest, hypotension, respiratory arrest, cardiac arrhythmias, hyperpyrexia, shivering, nausea, and emesis.

Dosage and Administration. FLUOTHANE may be administered by the nonrebreathing technic, partial rebreathing, or closed technic. The induction dose varies from patient to patient. The maintenance dose varies from 0.5 per cent to 1.5 per cent.

FLUOTHANE may be administered with either oxygen or a mixture of oxygen and nitrous oxide.

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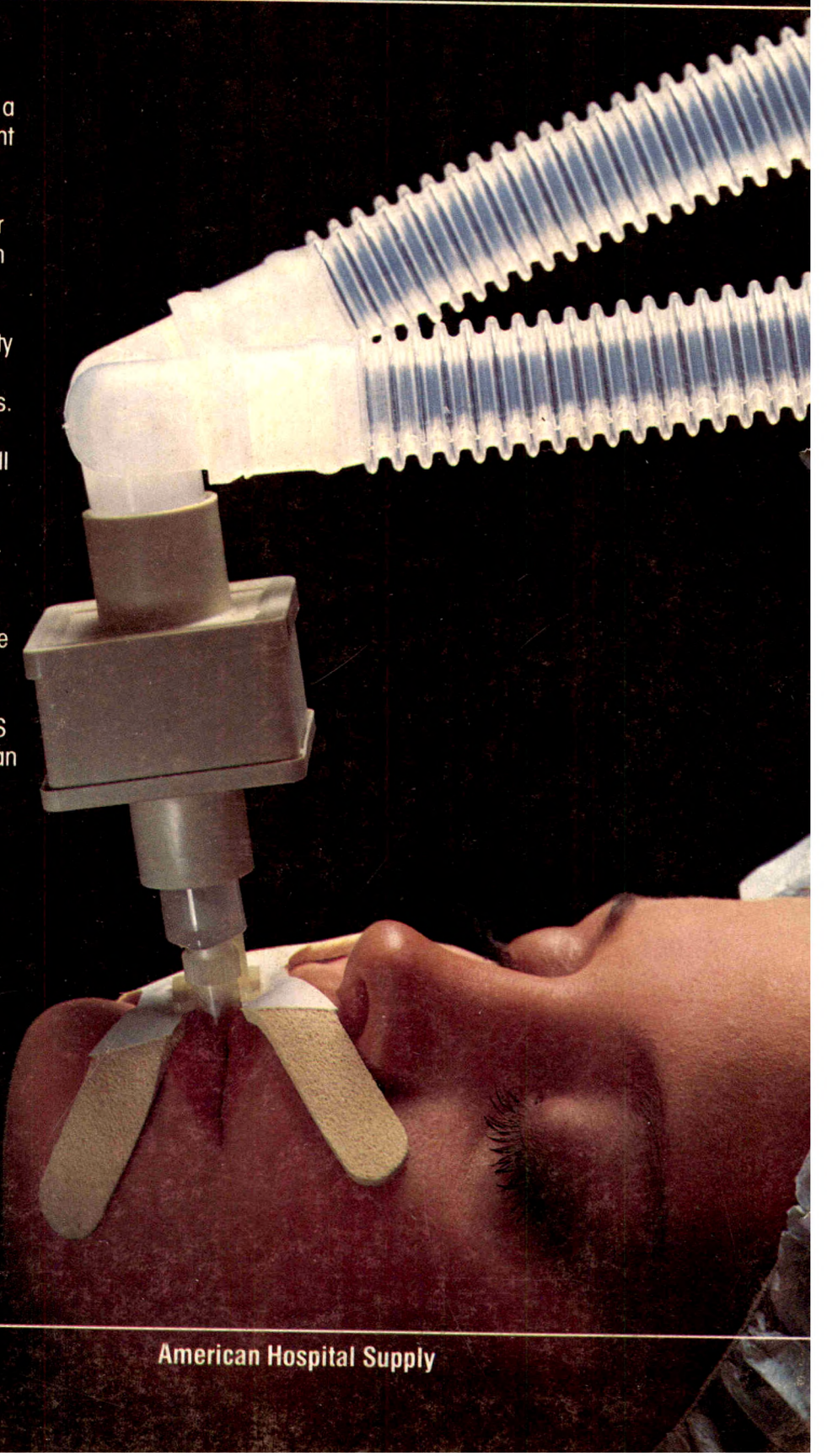
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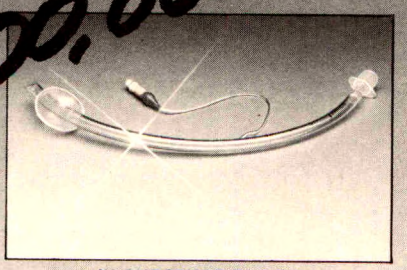
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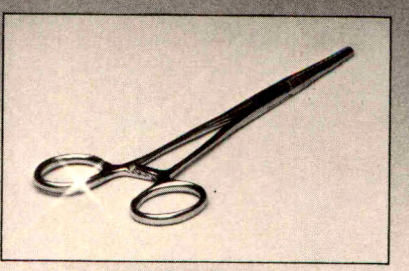
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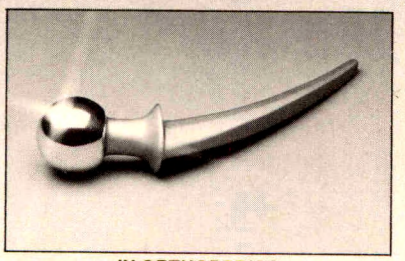
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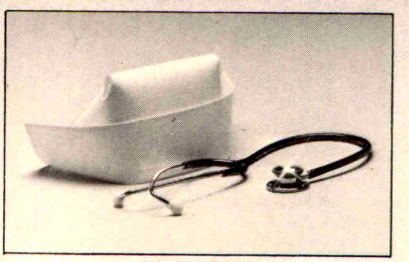
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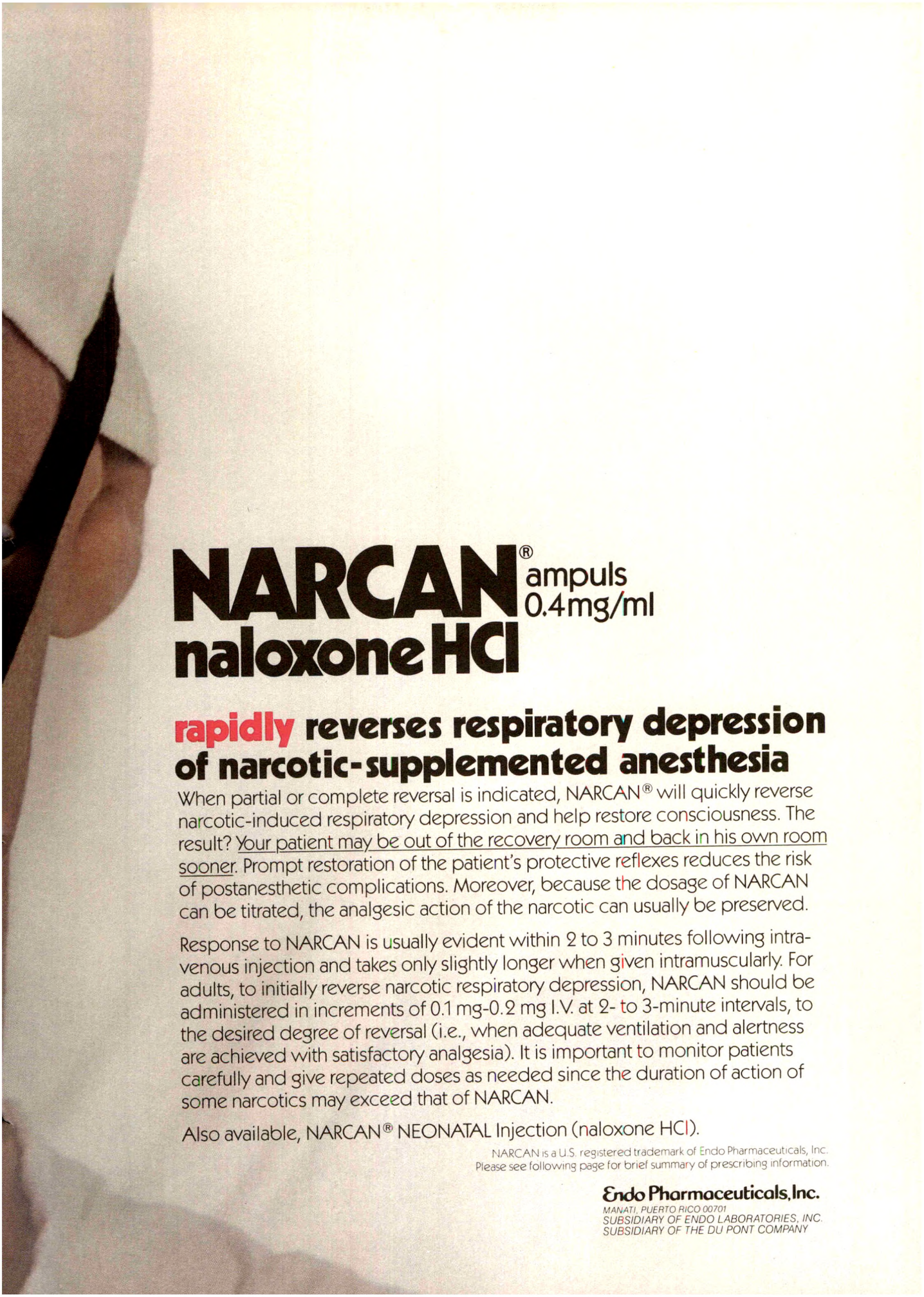
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The patient who has satisfactorily responded to NARCAN should be kept under continued surveillance and repeated doses of NARCAN should be administered, as necessary, since the duration of action of some narcotics may exceed that of NARCAN.

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PRECAUTIONS In addition to NARCAN, other resuscitative measures such as maintenance of a free airway, artificial ventilation, cardiac massage, and vasopressor agents should be available and employed when necessary to counteract acute narcotic poisoning. In an isolated report two patients with pre-existing ventricular irritability requiring lidocaine, and either isoproterenol or epinephrine for hypotension following cardiopulmonary bypass procedures, developed ventricular tachycardia or fibrillation when given NARCAN I.V. at 9 and 14 hours, respectively, postoperatively for persistent unresponsiveness. Although a direct cause and effect relationship has not been established, NARCAN should be used with caution in patients with cardiac irritability.

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Repeat doses of NARCAN may be required within one to two hour intervals depending upon the amount, type (i.e. short or long acting) and time interval since last administration of narcotic. Supplemental intramuscular doses have been shown to produce a longer lasting effect.

USAGE IN CHILDREN Narcotic Overdose—Known or Suspected: The usual initial child dose is 0.01 mg/kg body weight given I.V., I.M. or S.C. This dose may be repeated in accordance with the adult administration guideline. If necessary, NARCAN can be diluted with sterile water for injection.

USAGE IN NEONATES Narcotic-induced depression: The usual initial dose is 0.01 mg/kg body weight administered I.V., I.M. or S.C. This dose may be repeated in accordance with adult administration guidelines.

HOW SUPPLIED 0.4 mg/ml of NARCAN® (naloxone hydrochloride) for intravenous, intramuscular and subcutaneous administration.

Available in 1 ml ampuls in boxes of 10 and 100.

0.02 mg/ml of NARCAN® (naloxone hydrochloride) NEONATAL INJECTION for intravenous, intramuscular and subcutaneous administration.

Available in 2 ml ampuls in boxes of 10 and 100.

6077-4 BS

NARCAN is a U.S. registered trademark of Endo Pharmaceuticals, Inc.

Endo Pharmaceuticals, Inc.

MANATI, PUERTO RICO 00701

SUBSIDIARY OF ENDO LABORATORIES, INC

SUBSIDIARY OF THE DU PONT COMPANY

JEM 400 Guide Speeds Endotracheal Tube Changes



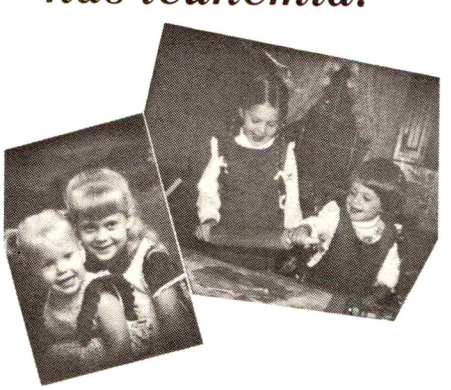
Endotracheal tube changing is greatly simplified through the use of the JEM 400 Guide Tube. Once replacement tube cuff is deflated and lubricated, adapter from patient's existing tube is removed and Guide is inserted through the E.T. lumen to the Guide mark. This aligns Guide tip with bevel of endotracheal tube. Stabilize Guide, deflate cuff, and remove old tube. New tube is then passed over Guide until proximal end is at Guide mark. Remove the Guide, reattach adapter, and inflate cuff. This procedure takes 30 to 120 seconds. A smooth, polished end minimizes risk of tracheal mucosal trauma. Write for additional information.

INSTRUMENTATION INDUSTRIES Inc.

1211 Streets Run Road, Pittsburgh, PA 15236

412 / 882-7711 or 884-5161

"My sister has leukemia."



It's terrible, but true, that children this young have learned to say this sentence. At St. Jude Children's Research Hospital we are trying to find the cause, cure and, ultimately, the prevention for cancer so no one will ever have to say these words again.

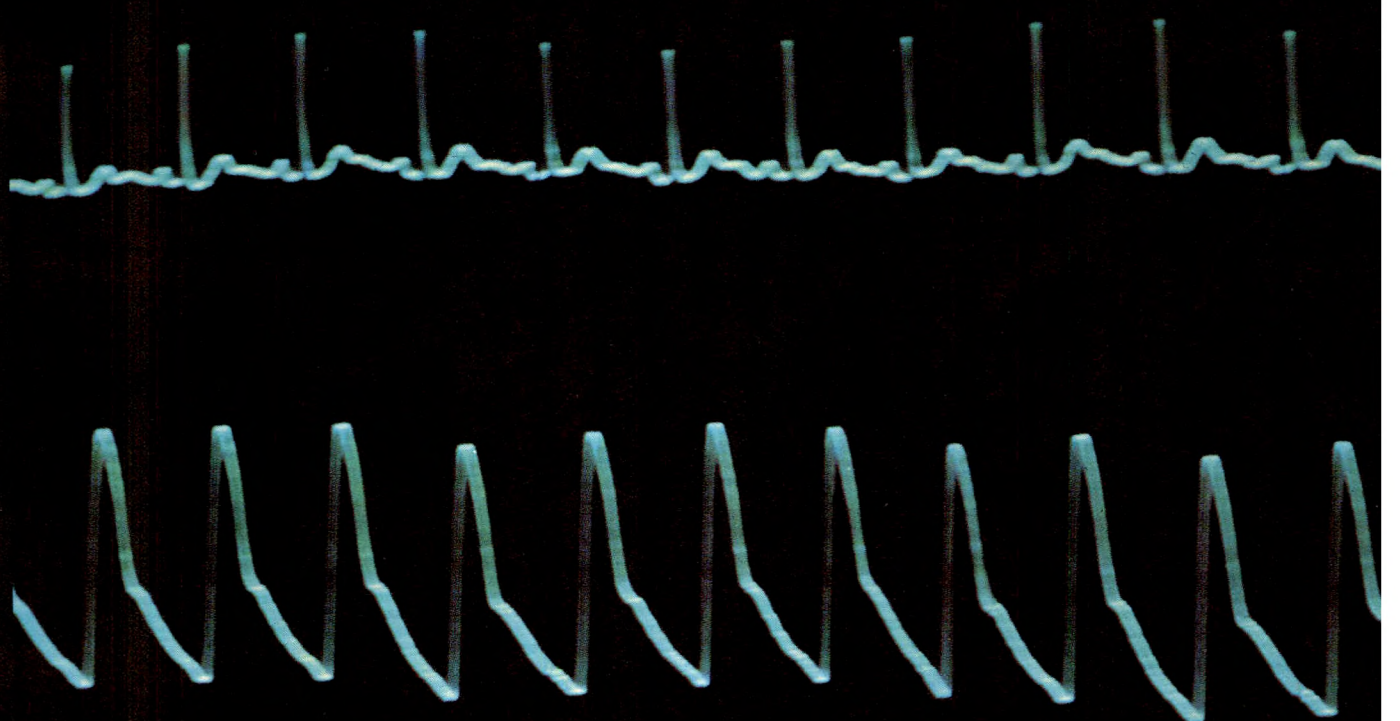
Please support the research at St. Jude. For more information, please write St. Jude, P.O. Box 3704, Memphis, Tennessee 38103, or call 1-800-238-9100.

ST. JUDE CHILDREN'S RESEARCH HOSPITAL

Danny Thomas, Founder

Announcing a new anesthetic concept

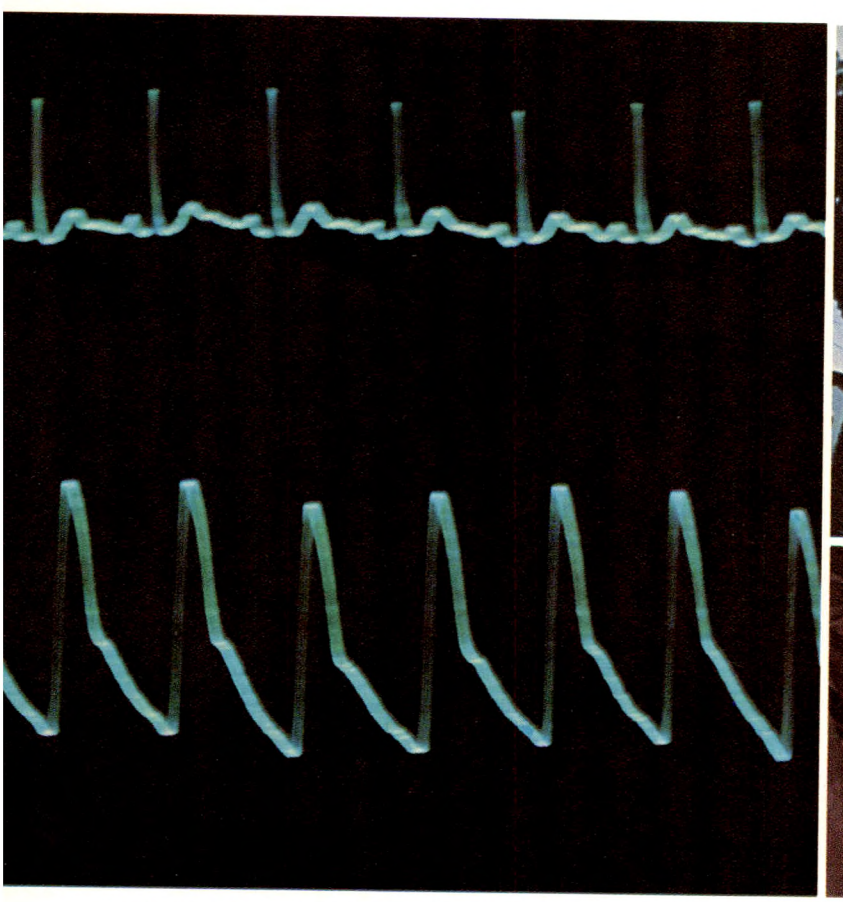
that provides maximum protection prior to maximum stress

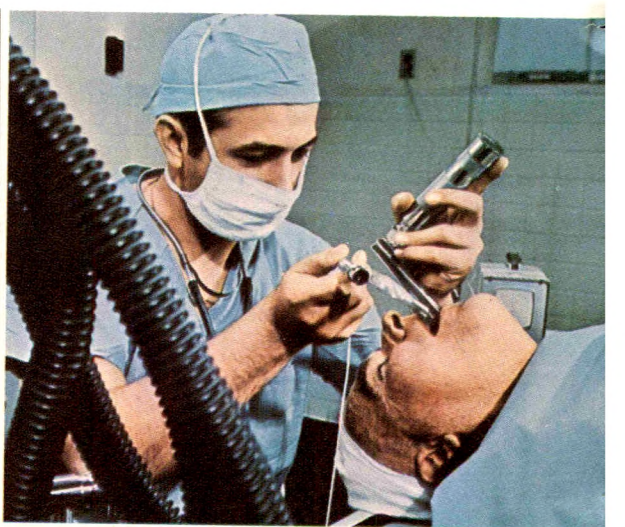


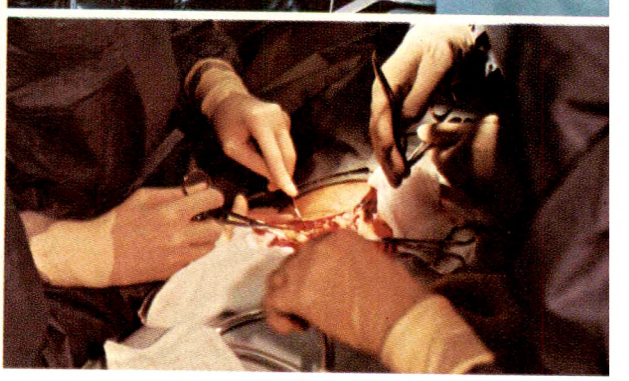
JANSSEN
PHARMACEUTICA

Introducing a new anesthetic technique:

This new technique—pre-induction analgesic loading—involves administering enough SUBLIMAZE® (fentanyl) *immediately before induction* to last generally the length of the procedure. Pre-induction upfront loading employs the pharmacokinetic properties of SUBLIMAZE® (fentanyl) to best advantage compared with p.r.n. use or administration of the drug incrementally throughout the procedure.







For further information and general guidelines on pre-induction analgesic loading with SUBLIMAZE® (fentanyl), please contact your Janssen representative or write Janssen Pharmaceutica.

JANSSEN PHARMACEUTICA

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Pre-induction analgesic loading with

Sublimaze®
(fentanyl) Injection C-II

1. Provides maximum protection just prior to anesthetic and surgical stress

Upfront loading immediately before induction puts the maximum amount of SUBLIMAZE® (fentanyl)* on board just prior to laryngoscopy, intubation and incision, the stimuli responsible for maximum stress. (SUBLIMAZE helps attenuate rises in blood pressure and pulse rate.)

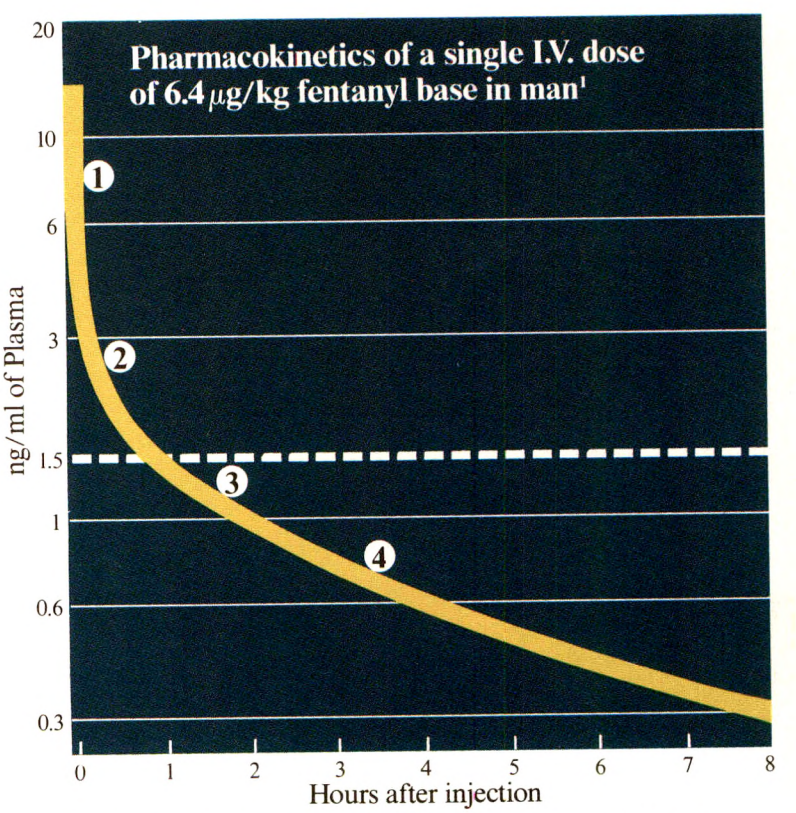
2. Eliminates "chasing the patient"

This new technique helps prevent sympathetic breakthrough and all the problems that stem from "chasing the patient."

3. Permits most patients to breathe spontaneously at completion of surgery

4. Reduces need for postoperative narcotics

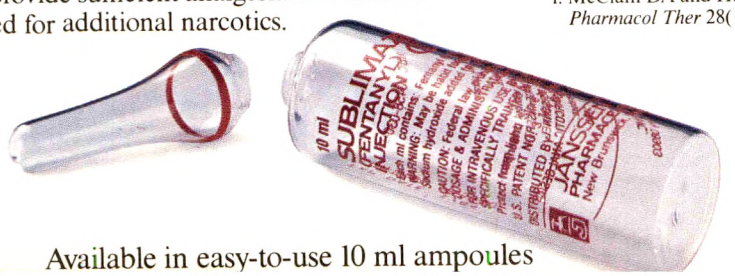
Postoperatively, residual plasma and tissue levels provide sufficient analgesia to minimize the need for additional narcotics.



Slightly depressed spontaneous respiration below 1.5 ng/ml; normal respiration below 0.7ng/ml.

***Note:** Respiratory depression may last longer than analgesic action and this risk increases with increasing doses.

1. McClain DA and Hug CC, Jr.: Intravenous fentanyl kinetics. *Clin Pharmacol Ther* 28(1): 106-114, 1980.



Available in easy-to-use 10 ml ampoules

Please see brief summary of Prescribing Information on next page.

Sublimaze®
(fentanyl) Injection

Protect from light. Store at room temperature.

Before prescribing, please consult complete prescribing information, of which the following is a brief summary.

FOR INTRAVENOUS OR INTRAMUSCULAR USE ONLY

DESCRIPTION

Each ml. contains:

Fentanyl ..... 50 mcg. (0.05 mg.) as the citrate

Warning: May be habit forming.

Sodium hydroxide for adjustment of pH to 4.0-7.5.

CONTRAINDICATIONS

SUBLIMAZE (fentanyl) is contraindicated in patients with known intolerance to the drug.

WARNINGS

AS WITH OTHER CNS DEPRESSANTS, PATIENTS WHO HAVE RECEIVED *SUBLIMAZE* (fentanyl) SHOULD HAVE APPROPRIATE SURVEILLANCE.

RESUSCITATION EQUIPMENT AND A NARCOTIC ANTAGONIST SHOULD BE READILY AVAILABLE TO MANAGE APNEA.

See also discussion of narcotic antagonists in Precautions and Overdosage.

If SUBLIMAZE (fentanyl) is administered with a tranquilizer such as *INAPSINE* (droperidol), the user should familiarize himself with the special properties of each drug, particularly the widely differing duration of action. In addition, when such a combination is used, *fluids and other countermeasures to manage hypotension should be available.*

As with other potent narcotics, the respiratory depressant effect of SUBLIMAZE (fentanyl) may persist longer than the measured analgesic effect. The total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, should be used in reduced doses initially, as low as 1/4 to 1/3 those usually recommended. SUBLIMAZE (fentanyl) may cause muscle rigidity, particularly involving the muscles of respiration. The effect is related to the speed of injection and its incidence can be reduced by the use of slow intravenous injection. Once the effect occurs, it is managed by the use of assisted or controlled respiration and, if necessary, by a neuromuscular blocking agent compatible with the patient's condition. Where moderate or high doses are used (above 10 mcg./kg.), there must be adequate facilities for postoperative observation, and ventilation if necessary, of patients who have received SUBLIMAZE (fentanyl). It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

Drug Dependence—SUBLIMAZE (fentanyl) can produce drug dependence of the morphine type and, therefore, has the potential for being abused.

Severe and unpredictable potentiation by MAO inhibitors has been reported with narcotic analgesics. Since the safety of fentanyl in this regard has not been established, the use of SUBLIMAZE (fentanyl) in patients who have received MAO inhibitors within 14 days is not recommended.

Head Injuries and Increased Intracranial Pressure—SUBLIMAZE (fentanyl) should be used with caution in patients who may be particularly susceptible to respiratory depression, such as comatose patients who may have a head injury or brain tumor. In addition SUBLIMAZE (fentanyl) may obscure the clinical course of patients with head injury.

Usage in Children—The safety of SUBLIMAZE (fentanyl) in children younger than two years of age has not been established.

Usage in Pregnancy—The safe use of SUBLIMAZE (fentanyl) has not been established with respect to possible adverse effects upon fetal development. Therefore, it should be used in women of childbearing potential only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. There are insufficient data regarding placental transfer and fetal effects; therefore, safety for the infant in obstetrics has not been established.

PRECAUTIONS

The initial dose of SUBLIMAZE (fentanyl) should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining incremental doses. Nitrous oxide has been reported to produce cardiovascular depression when given with higher doses of fentanyl.

Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can alter respiration by blocking intercostal nerves. Through other mechanisms SUBLIMAZE (fentanyl) can also alter respiration. Therefore, when SUBLIMAZE (fentanyl) is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for these forms of anesthesia.

When used with a tranquilizer such as *INAPSINE* (droperidol), blood pressure may be altered and hypotension can occur.

Vital signs should be monitored routinely.

SUBLIMAZE (fentanyl) should be used with caution in patients with chronic obstructive pulmonary disease, patients with decreased respiratory reserve, and others with potentially compromised respiration. In such patients, narcotics may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Respiratory depression caused by narcotic analgesics can be reversed by narcotic antagonists. Appropriate surveillance should be maintained because the duration of respiratory depression of doses of fentanyl employed during anesthesia may be longer than the duration of the narcotic antagonist action. Consult individual prescribing information (levallorphan, nalorphine and naloxone) before employing narcotic antagonists.

When a tranquilizer such as *INAPSINE* (droperidol) is used with SUBLIMAZE (fentanyl) pulmonary arterial pressure may be decreased. This fact should be considered by those who conduct diagnostic and surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient. When high dose or anesthetic dosages of SUBLIMAZE (fentanyl) are employed, even relatively small dosages of diazepam may cause cardiovascular depression.

Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, and general anesthetics) will have additive or potentiating effects with SUBLIMAZE (fentanyl). When patients have received such drugs, the dose of SUBLIMAZE (fentanyl) required will be less than usual. Likewise, following the administration of SUBLIMAZE (fentanyl), the dose of other CNS depressant drugs should be reduced.

SUBLIMAZE (fentanyl) should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.

SUBLIMAZE (fentanyl) may produce bradycardia, which may be treated with atropine; however, SUBLIMAZE (fentanyl) should be used with caution in patients with cardiac bradyarrhythmias.

When SUBLIMAZE (fentanyl) is used with a tranquilizer such as *INAPSINE* (droperidol) hypotension can occur. If this occurs, the possibility of hypovolemia should also be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should be considered when operative conditions permit. Care should be exercised in moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do not correct hypotension, the administration of pressor agents other than epinephrine should be considered. Because of the alpha-adrenergic blocking action of *INAPSINE* (droperidol), epinephrine may paradoxically decrease the blood pressure in patients treated with *INAPSINE* (droperidol).

When *INAPSINE* (droperidol) is used with SUBLIMAZE (fentanyl) and the EEG is used for postoperative monitoring, it may be found that the EEG pattern returns to normal slowly.

ADVERSE REACTIONS

As with other narcotic analgesics, the most common serious adverse reactions reported to occur with SUBLIMAZE (fentanyl) are respiratory depression, apnea, muscular rigidity, and bradycardia; if these remain untreated, respiratory arrest, circulatory depression or cardiac arrest could occur. Other adverse reactions that have been reported are hypotension, dizziness, blurred vision, nausea, emesis, laryngospasm, and diaphoresis.

It has been reported that secondary rebound respiratory depression may occasionally occur postoperatively. Patients should be monitored for this possibility and appropriate countermeasures taken as necessary.

When a tranquilizer such as *INAPSINE* (droperidol) is used with SUBLIMAZE (fentanyl), the following adverse reactions can occur: chills and/or shivering, restlessness, and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression); extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed up to 24 hours postoperatively. When they occur, extrapyramidal symptoms can usually be controlled with anti-parkinson agents. Postoperative drowsiness is also frequently reported following the use of *INAPSINE* (droperidol).

Elevated blood pressure, with and without pre-existing hypertension, has been reported following administration of SUBLIMAZE (fentanyl) combined with *INAPSINE* (droperidol). This might be due to unexplained alterations in sympathetic activity following large doses; however, it is also frequently attributed to anesthetic and surgical stimulation during light anesthesia.

DOSAGE AND ADMINISTRATION

50 mcg. = .05 mg. = 1 ml.

Dosage should be individualized. Some of the factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and the surgical procedure involved.

Vital signs should be monitored routinely.

I. *Premedication*—Premedication (to be appropriately modified in the elderly, debilitated, and those who have received other depressant drugs)—50 to 100 mcg. (0.05 to 0.1 mg.)(1 to 2 ml.) may be administered *intramuscularly* 30 to 60 minutes prior to surgery.

II. *Adjunct to General Anesthesia*—See Dosage Range Chart

III. *Adjunct to Regional Anesthesia*—50 to 100 mcg. (0.05 to 0.1 mg.)(1 to 2 ml.) may be administered intramuscularly or slowly intravenously, over one to two minutes, when additional analgesia is required.

IV. *Postoperatively (recovery room)*—50 to 100 mcg. (0.05 to 0.1 mg.)(1 to 2 ml.) may be administered intramuscularly for the control of pain, tachypnea and emergence delirium. The dose may be repeated in one to two hours as needed.

Usual Children's Dosage: For induction and maintenance in children 2 to 12 years of age, a reduced dose as low as 20 to 30 mcg. (0.02 to 0.03 mg.)(0.4 to 0.6 ml.) per 20 to 25 pounds is recommended.

DOSAGE RANGE CHART

TOTAL DOSAGE

Low dose—2 mcg./kg. (.002 mg./kg.) (.04 ml./kg.) SUBLIMAZE® injection. Fentanyl in small doses is most useful for minor, but painful, surgical procedures. In addition to the analgesia during surgery, fentanyl may also provide some pain relief in the immediate postoperative period. *Maintenance:* Additional dosages of SUBLIMAZE® injection are infrequently needed in these minor procedures.

Moderate dose—2-20 mcg./kg. (.002-.02 mg./kg.)(.04-0.4 ml./kg.) SUBLIMAZE® injection. Where surgery becomes more major, a larger dose is required. With this dose, in addition to adequate analgesia, one would expect to see some abolition of the stress response. However, respiratory depression will be such that artificial ventilation during anesthesia is necessary, and careful observation of ventilation postoperatively is essential. *Maintenance:* 25 to 100 mcg. (0.025 to 0.1 mg.)(0.5 to 2.0 ml.) may be administered intravenously or intramuscularly when movement and/or changes in vital signs indicate surgical stress or lightening of analgesia.

High dose—20-50 mcg./kg. (.02-.05 mg./kg.)(0.4-1 ml./kg.) SUBLIMAZE® injection. During open heart surgery and certain more complicated neurosurgical and orthopedic procedures where surgery is more prolonged, and in the opinion of the anesthesiologist, the stress response to surgery would be detrimental to the well being of the patient, dosages of 20-50 mcg./kg. (.02-.05 mg.)(0.4-1 ml.) of SUBLIMAZE® injection with nitrous oxide oxygen have been shown to attenuate the stress response as defined by increased levels of circulating growth hormone, catecholamine, ADH, and prolactin.

When dosages in this range have been used during surgery, postoperative ventilation and observation are essential due to extended postoperative respiratory depression.

The main objective of this technique would be to produce "stress free" anesthesia. *Maintenance:* Maintenance dosage (ranging from 25 mcg. (.025 mg.)(0.5 ml.) to one half the initial loading dose) will be dictated by the changes in vital signs which indicate stress and lightening of analgesia. However, the additional dosage selected must be individualized especially if the anticipated remaining operative time is short.

As a General Anesthetic

When attenuation of the responses to surgical stress is especially important, doses of 50 to 100 mcg./kg. (.05 to 0.1 mg./kg.)(1 to 2 ml./kg.) may be administered with oxygen and a muscle relaxant. This technique has been reported to provide anesthesia without the use of additional anesthetic agents. In certain cases, doses up to 150 mcg./kg. (.15 mg./kg.)(3 ml./kg.) may be necessary to produce this anesthetic effect. It has been used for open heart surgery and certain other major surgical procedures in patients for whom protection of the myocardium from excess oxygen demand is particularly indicated, and for certain complicated neurological and orthopedic procedures.

As noted above, it is essential that qualified personnel and adequate facilities be available for the management of respiratory depression.

See Warnings and Precautions for use of SUBLIMAZE (fentanyl) with other CNS depressants, and in patients with altered response.

OVERDOSAGE

Manifestations: The manifestations of SUBLIMAZE (fentanyl) overdosage are an extension of its pharmacologic actions.

Treatment: In the presence of hypoventilation or apnea, oxygen should be administered and respiration should be assisted or controlled as indicated. A patent airway must be maintained; and oropharyngeal airway or endotracheal tube might be indicated. If depressed respiration is associated with muscular rigidity, an intravenous neuromuscular blocking agent might be required to facilitate assisted or controlled respiration. The patient should be carefully observed for 24 hours; body warmth and adequate fluid intake should be maintained. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. A specific narcotic antagonist such as nalorphine, levallorphan, or naloxone should be available for use as indicated to manage respiratory depression. This does not preclude the use of more immediate countermeasures. The duration of respiratory depression following overdosage of fentanyl may be longer than the duration of narcotic antagonist action. Consult the package insert of the individual narcotic antagonists for details about use.

HOW SUPPLIED

2 ml. and 5 ml. ampoules—packages of 10.
NDC 50458-030-02 **NDC** 50458-030-05

10 ml. and 20 ml. ampoules—packages of 5.
NDC 50458-030-10 **NDC** 50458-030-20
(For intravenous use by hospital personnel specifically trained in the use of narcotic analgesics).

March, 1980. Revised June, 1980. January, 1981
U.S. Patent No. 3, 164 600



world leader in anesthesia research

JANSSEN
PHARMACEUTICA

Janssen Pharmaceutica Inc., 501 George St., New Brunswick, N.J. 08903

JPI-255

For one of medicine's most demanding skills... one of medicine's most dependable agents



precise control . . . stability of heart rhythm . . .
reduced relaxant requirement . . . prompt, smooth recovery
. . . organ toxicity rare or nonexistent

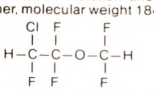
Ohio Medical Anesthetics

Ethrane® (enflurane)

CAUTION: Federal Law Prohibits Dispensing without Prescription.

DESCRIPTION

ETHRANE (enflurane) is a nonflammable inhalation anesthetic agent. It is 2-chloro-1, 1,2-trifluoroethyl difluoromethyl ether, molecular weight 184.5, and its structural formula is:



The boiling point is 56.5°C at 760 mm Hg and the vapor pressure (mm Hg) is 175 at 20°C, 218 at 25°C, and 345 at 36°C. Vapor pressures can be calculated using the equation:

$\log_{10}P=A+B/T$ $A=7.967$

$B=-1678.4$

$T=°C+273.16$ (Kelvin)

The specific gravity (25°/25°C) is 1.517. The refractive index at 20° is 1.3026-1.3030. The blood/gas coefficient is 1.91 at 37°C and the oil/gas coefficient is 98.5 at 37°C. The M.A.C. (minimum alveolar concentration) in man is 1.68 percent in pure oxygen, 0.57 in 70% nitrous oxide and oxygen, and 1.17 in 30% nitrous oxide and oxygen.

ETHRANE is a clear, colorless, stable liquid whose purity exceeds 99.9 percent (area % by gas chromatography). No chemical stabilizers are added as these have been found, through controlled laboratory tests, to be unnecessary to maintain stability even in the presence of ultraviolet light. ETHRANE is stable to strong base and does not decompose in contact with soda lime and does not attack aluminum, tin, brass, iron or copper. The partition coefficients of ETHRANE at 25°C are 74 in conductive rubber and 120 in polyvinyl chloride.

CLINICAL PHARMACOLOGY

ETHRANE (enflurane) is an inhalation anesthetic. Induction and recovery from anesthesia with ETHRANE are rapid. ETHRANE has a mild, sweet odor. There is mild stimulus to salivation or tracheobronchial secretions when ETHRANE is used alone. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia changes rapidly with ETHRANE. ETHRANE reduces ventilation as depth of anesthesia increases. High pCO_2 levels can be obtained at deeper levels of anesthesia if ventilation is not supported. ETHRANE provokes a sigh response reminiscent of that seen with diethyl ether.

There is a decrease in blood pressure with induction of anesthesia, followed by a return to near normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding increases in hypotension. Heart rate remains relatively constant without significant bradycardia. Electrocardiographic monitoring or recordings indicate that cardiac rhythm remains stable. Elevation of the carbon dioxide level in arterial blood does not alter cardiac rhythm.

Studies in man indicate a considerable margin of safety in the administration of epinephrine containing solutions during ETHRANE anesthesia. ETHRANE anesthesia has been used in excision of pheochromocytoma in man without ventricular arrhythmias. On the basis of studies in patients anesthetized with ETHRANE and injected with epinephrine containing solutions to achieve hemostasis in a highly vascular area (transphenoidal surgery), it is recommended that 2 micrograms per kilogram (2μg/kg) of epinephrine may be injected subcutaneously over a 10 minute period. This may be repeated up to 3 times per hour.

Example: Up to 10 ml of 1:100,000 epinephrine containing solution (10μg/ml) may be injected subcutaneously over a 10 minute period in a 50 kilogram patient judged to have ordinary tolerance to epinephrine administration. No more than 30 ml of 1:100,000 epinephrine containing solution (10μg/ml) should be administered to such a patient per hour. The concomitant administration of lidocaine enhances the safety of the use of epinephrine during ETHRANE anesthesia. This effect of lidocaine is dose related. All customary precautions in the use of vasoconstrictor substances should be observed.

Example Two: Alternatively, up to 20 ml of 1:200,000 epinephrine containing solution (5 μg/ml) may be substituted for 10 ml of 1:100,000 solution in the above example.

Muscle relaxation may be adequate for intra-abdominal operation at normal levels of anesthesia. Muscle relaxants may be used to achieve greater relaxation and all commonly used muscle relaxants are compatible with ETHRANE. The NONDEPOLARIZING MUSCLE RELAXANTS ARE POTENTIATED. In the normal 70 kg adult, 6 to 9 mg of d-tubocurarine or 1 to 1.5 mg of pancuronium will produce a 90 percent or greater depression of twitch height. Neostigmine does not reverse the direct effect of ETHRANE.

Biotransformation of ETHRANE in man results in low levels of serum fluoride ions averaging 15 μM/L. These levels are well below the 50 μM/L threshold level which can produce minimal renal damage in normal subjects; however, it is possible that these levels could result in damage in patients with severely impaired renal function or those undergoing renal transplantation. Depression of lymphocyte transformation does not follow prolonged ETHRANE anesthesia in man in the absence of surgery. Thus ETHRANE does not depress this aspect of the immune response.

INDICATIONS

ETHRANE (enflurane) may be used for induction and maintenance of general anesthesia. Adequate data have not been developed to establish its application in obstetrical anesthesia.

CONTRAINDICATIONS

Seizure disorders (see WARNINGS).

Known sensitivity to ETHRANE (enflurane) or other halogenated anesthetics.

WARNINGS

Increasing depth of anesthesia with ETHRANE (enflurane) may produce a change in the electroencephalogram characterized by high voltage, fast frequency, progressing through spike-dome complexes alternating with periods of electrical silence to frank seizure activity. The latter may or may not be associated with motor movement. Motor activity, when encountered, generally consists of twitching or jerks of various muscle groups; it is self-limiting and can be terminated by lowering the anesthetic concentration. This electroencephalographic pattern associated with deep anesthesia is exacerbated by low arterial carbon dioxide tension. A reduction in ventilation and anesthetic concentration usually suffices to eliminate seizure activity. Cerebral blood flow and metabolism studies in normal volunteers immediately following seizure activity show no evidence of cerebral hypoxia. Mental function testing does not reveal any impairment of performance following prolonged ETHRANE anesthesia associated with or not associated with seizure activity.

Since levels of anesthesia may be altered easily and rapidly, only calibrated vaporizers which measure output with reasonable accuracy should be used. Hypotension and respiratory exchange can serve as a guide to anesthesia depth. Deep levels of anesthesia may produce marked hypotension and respiratory depression.

The action of nondepolarizing relaxants is augmented by ETHRANE. Less than the usual amounts of these drugs should be used. If the usual amounts of nondepolarizing relaxants are given, the time for recovery from myoneural blockade will be longer in the presence of ETHRANE than for other commonly used anesthetics.

Usage in Pregnancy: Safety in pregnancy has not been established. Reproduction studies have been performed in rats and rabbits, and there is no evidence of harm to the animal fetus. The relevance of these studies to the human is not known. Since there is no adequate experience in pregnant women who have received the drug, safety in pregnancy has not been established.

PRECAUTIONS

Bromsulfalein (BSP) retention is mildly elevated postoperatively in some cases. This may relate to the effect of surgery since prolonged anesthesia (5 to 7 hours) in human volunteers does not result in BSP elevation. There is some elevation of glucose and white blood count intraoperatively. Glucose elevation should be considered in diabetic patients. ETHRANE (enflurane) should be used with caution in patients who by virtue of medical or drug history could be considered more susceptible to cortical stimulation produced by this drug. As with other general anesthetics and some muscle relaxants, hyperpyrexia has been observed with the use of ETHRANE.

ADVERSE REACTIONS

1. Motor activity examplified by movements of various muscle groups and/or seizures may be encountered with deep levels of ETHRANE (enflurane) anesthesia, or light levels with hypocapnia.
2. Hypotension and respiratory depression have been reported.
3. Arrhythmias, shivering, nausea, and vomiting have been reported.
4. Elevation of the white blood count has been observed.

DOSAGE AND ADMINISTRATION

The concentration of ETHRANE (enflurane) being delivered during anesthesia from a vaporizer should be known. This may be accomplished by using:

a) vaporizers calibrated specifically for ETHRANE.

b) vaporizers from which delivered flows can easily and readily be calculated.

Nothing is present in the agent to alter calibration or affect the operation characteristics of the vaporizer.

Preanesthetic Medication: Preanesthetic medication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by ETHRANE and the heart rate remains constant; the use of anticholinergic drugs is a matter of choice.

Induction: Induction may be achieved using ETHRANE alone with oxygen or in combination with oxygen-nitrous oxide mixtures. Under these conditions some excitement may be encountered. If excitement is to be avoided, a hypnotic dose of a short-acting barbiturate should be used to induce unconsciousness, followed by the ETHRANE mixture. In general, inspired concentrations of 2.0-4.5% ETHRANE produce surgical anesthesia in 7-10 minutes.

Maintenance: Surgical levels of anesthesia may be maintained with 0.5-3% ETHRANE. Maintenance concentrations should not exceed 3%. If added relaxation is required, supplemental doses of muscle relaxants may be used. Ventilation to maintain the tension of carbon dioxide in arterial blood in the 35-45 mm Hg range is preferred. Hyperventilation should be avoided in order to minimize possible CNS excitation.

The level of blood pressure during maintenance is an inverse function of ETHRANE concentration in the absence of other complication problems. Excessive decreases (unless related to hypovolemia) may be due to depth of anesthesia and in such instances should be corrected by lightening the level of anesthesia.

Overdosage: In the event of overdosage, or what may appear to be overdosage, the following action should be taken.

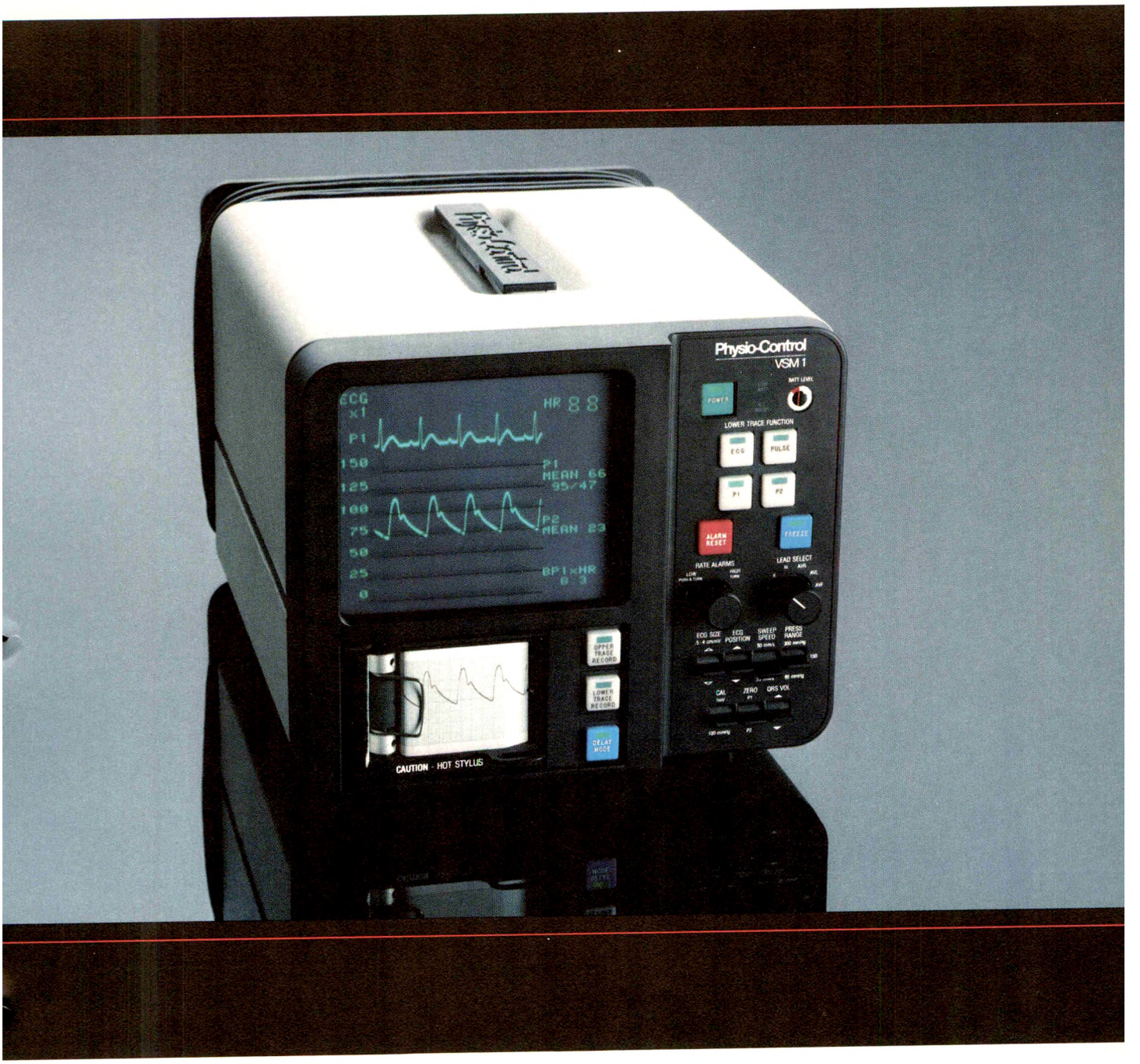
Stop drug administration; establish a clear airway and initiate assisted or controlled ventilation with pure oxygen.

PACKAGING

ETHRANE (enflurane) is packaged in 125 and 250 ml amber colored bottles.

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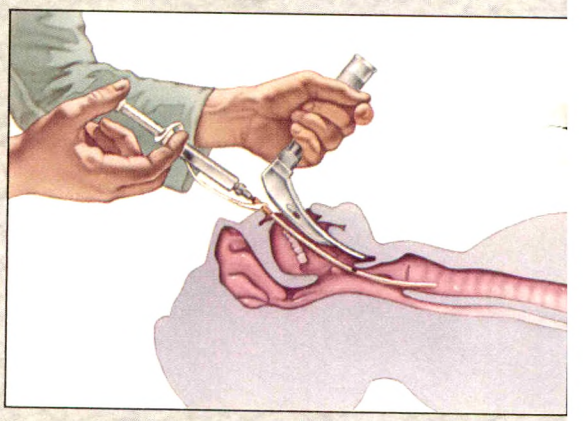
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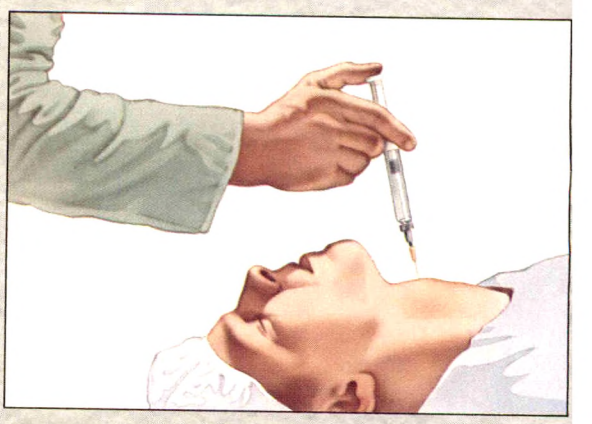
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Lets you choose the intraoral or transtracheal route of administration

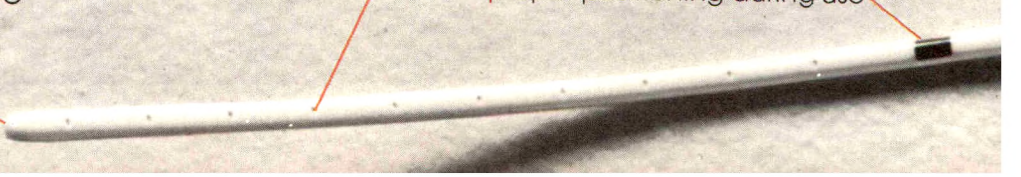
☐ The anatomically curved cannula provided, conveniently allows administration via the intraoral approach.

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10 jets ATOP cannula
- upward spray ensures 360° coverage
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- covers tracheo-bronchial junction



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A sterile, disposable, prefilled syringe and cannula kit for convenient laryngotracheal anesthesia prior to intubation, diagnosis, surgery.



25% more drug than other kits*

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- marked in 1/2 ml increments to aid in proper dose determination and accuracy of drug delivery

Prefilled syringe

- totally sterile and self-contained
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- a simple twist quickly activates the syringe and readies the unit for attachment of cannula or needle

Luer hub

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Cannula

- anatomically curved to facilitate introduction into larynx and trachea.
- easily attaches to syringe, virtually no assembly time

*Although absorption of lidocaine from respiratory mucosa varies widely among individuals, blood concentrations achieved by this route can rise to levels comparable to those reached by similar doses infused intravenously, and in some cases almost as rapidly.[1,2,3]

REFERENCES

1. Bromage P: Concentrations of lidocaine in the blood after intravenous and endotracheal administration. *Anaesthesia*, 16:461, 1961.
2. Chu S: Plasma concentration of lidocaine after endotracheal spray. *Anesth. Analg.*, 54:438, 1975.
3. Pelton D: Plasma lidocaine concentrations following topical aerosol application to the trachea and bronchi. *Canad. Anaesth. Soc. J.*, 17:250, 1970.

ASTRA®

Astra Pharmaceutical Products, Inc.
Worcester, Massachusetts 01606

(Please see following page for a brief summary of prescribing information.)

Xylocaine®
(lidocaine hydrochloride)
4% Sterile Solution

Before prescribing or administering, please consult complete product information, a summary of which follows:

CONTRAINDICATIONS: Lidocaine hydrochloride sterile solution is contraindicated in patients with a known history of hypersensitivity either to local anesthetics of the amide type or to other components of the sterile solution.

PRECAUTIONS: The safety and effectiveness of lidocaine hydrochloride depend on proper dosage, correct technique, adequate precautions, and readiness for emergencies. Standard textbooks should be consulted for specific techniques and precautions for various anesthetic procedures.

The lowest dosage that results in effective anesthesia should be used. Injection of repeated doses of lidocaine hydrochloride may cause significant increases in blood levels with each repeated dose due to slow accumulation of the drug or its metabolites. Tolerance varies with the status of the patient. Debilitated, elderly patients, acutely ill patients, and children should be given reduced doses commensurate with their age and physical status. Lidocaine hydrochloride should also be used with caution in patients with severe shock or heart block.

As with all injections of local anesthetics, retrobulbar injection should always be made slowly and with frequent aspirations.

Solutions to which a vasoconstrictor has been added should be used with caution in the presence of diseases which may adversely affect the patient's cardiovascular system. Serious cardiac arrhythmias may occur if preparations containing a vasoconstrictor are employed in patients during or following the administration of chloroform, halothane, cyclopropane, trichlorethylene, or other related agents.

Lidocaine hydrochloride should be used with caution in persons with known drug sensitivities. Patients allergic to para-aminobenzoic acid derivatives (procaine, tetracaine, benzocaine, etc.) have not shown cross sensitivity to lidocaine HCl.

Local anesthetics react with certain metals and cause the release of their respective ions which, if injected, may cause severe local irritation. Adequate precaution should be taken to avoid this type of interaction.

The safety of amide local anesthetics in patients with malignant hyperthermia has not been assessed, and therefore, those agents should be used with caution in such patients.

Drowsiness following lidocaine hydrochloride injection is *usually* an early indication of a high blood level of the drug and may occur following inadvertent intravascular administration or *rapid absorption* of lidocaine.

ADVERSE REACTIONS: Adverse reactions may result from high plasma levels due to excessive dosage, rapid absorption or inadvertent intravascular injection. Such reactions are systemic in nature and involve the central nervous system and/or the cardiovascular system. A small number of reactions may result from hypersensitivity, idiosyncrasy or diminished tolerance on the part of the patient.

CNS reactions are excitatory and/or depressant, and may be characterized by nervousness, dizziness, blurred vision and tremors, followed by drowsiness, convulsions, unconsciousness and possibly respiratory arrest. The excitatory reactions may be very brief or may not occur at all, in which case the first manifestations of toxicity may be drowsiness, merging into unconsciousness and respiratory arrest.

Toxic cardiovascular reactions to local anesthetics are usually depressant in nature and are characterized by hypotension, myocardial depression, bradycardia and possibly cardiac arrest.

Treatment of a patient with toxic manifestations consists of assuring and maintaining a patent airway, supporting ventilation with oxygen, and assisted or controlled ventilation (respiration) as required. This usually will be sufficient in the management of most reactions. Should a convulsion persist despite ventilation therapy, small increments of anticonvulsive agents may be given intravenously. Examples of such agents include benzodiazepine (e.g., diazepam), ultrashort acting barbiturates (e.g., thiopental or thiamylal) or a short acting barbiturate (e.g., pentobarbital or secobarbital). Cardiovascular depression may require circulatory assistance with intravenous fluids and/or vasopressors (e.g., ephedrine) as dictated by the clinical situation.

Allergic reactions may occur as a result of sensitivity either to local anesthetics or to other components of the sterile solution. Anaphylactoid type symptomatology and reactions, characterized by cutaneous lesions, urticaria, edema, should be managed by conventional means. The detection of potential sensitivity by skin testing is of limited value.

HOW SUPPLIED: Xylocaine (lidocaine hydrochloride) 4% Sterile Solution: 5 ml ampule, package of 10; 5 ml prefilled sterile disposable syringe.

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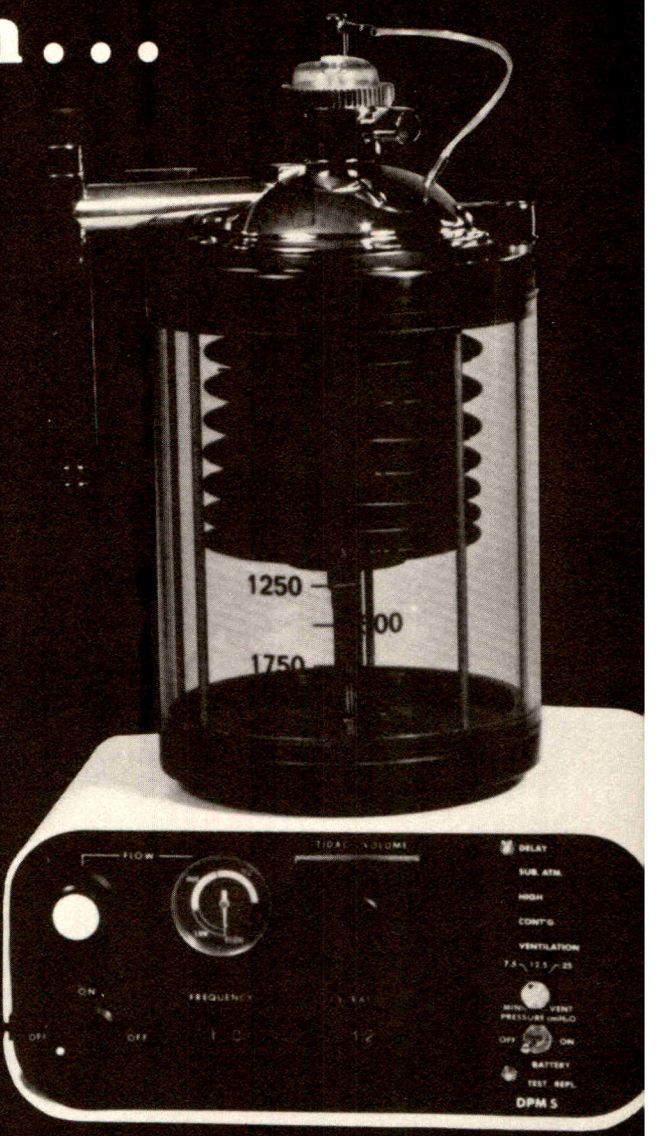
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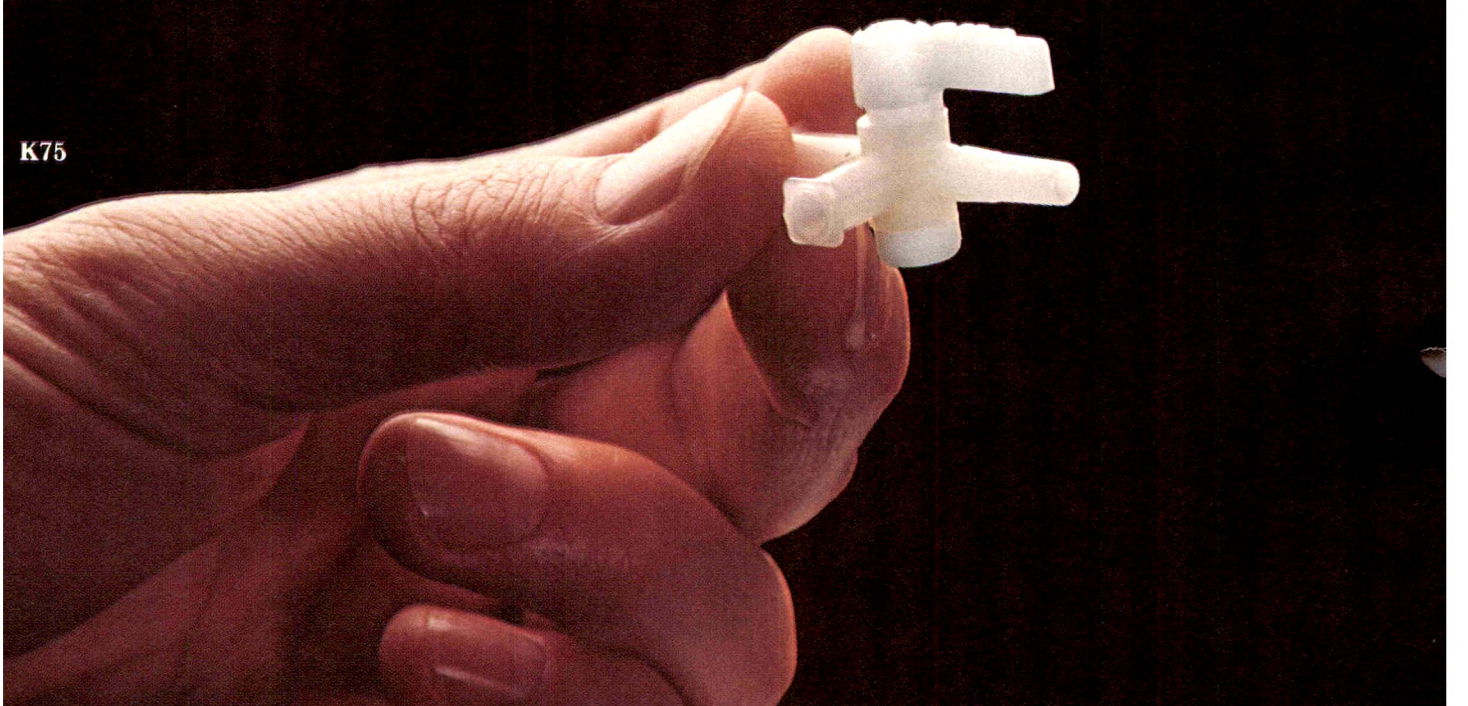
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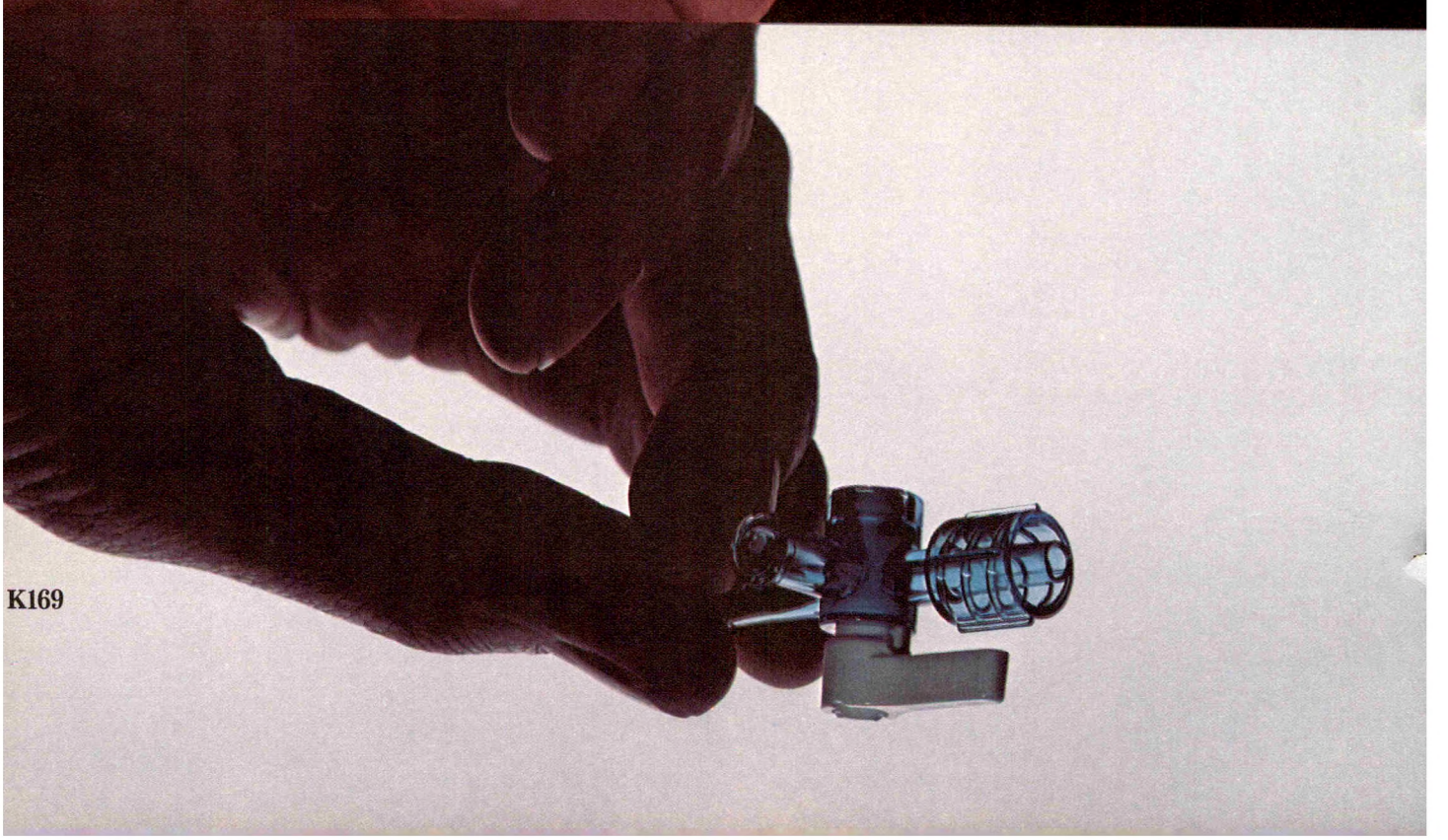
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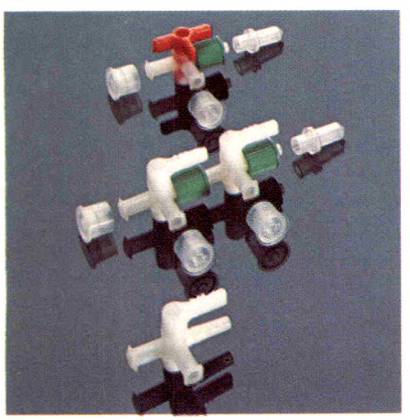
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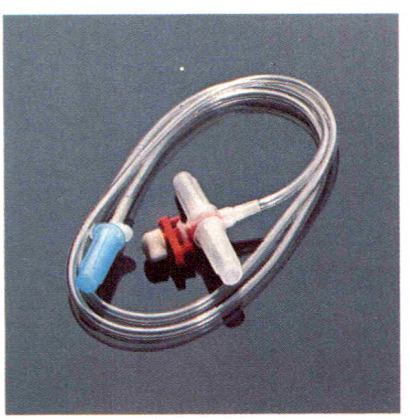
Our K-75 and K-52 Novex® stopcocks are legendary. And they're only part of the most complete and widely used line of general purpose stopcocks available anywhere.

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Stopcocks with special caps to protect ports. And with rotating Luer-lock adapters for proper alignment and secure connections.





Stopcocks with a choice of pre-attached extension tubes which add up to a virtually endless variety of possible applications.

All with smooth-turning handles that won't stick or leak in the usual applications.

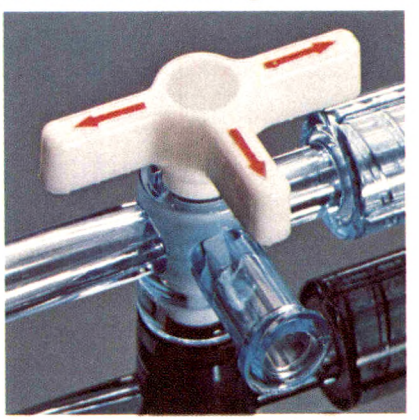
And now, a complete line of K-Series clear stopcocks for invasive monitoring.

Our latest innovation is the K-Series clear stopcocks designed for invasive monitoring.

The transparent light blue body makes air bubbles very easy to see with visual inspection. So there's no need to worry about hidden air bubbles.

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These non-leaking stopcocks feature Luer-lock fittings. They're superb units, just what you need for invasive monitoring.



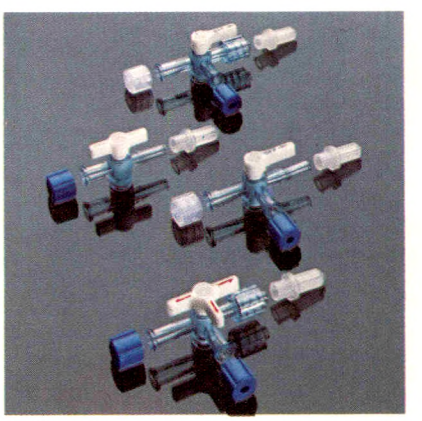
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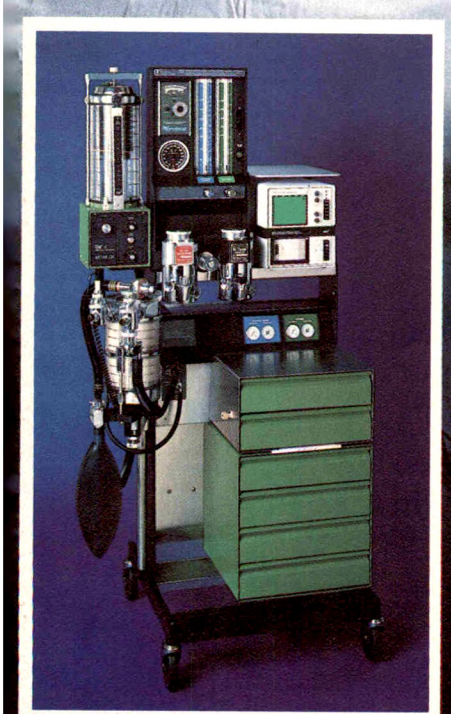


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Long before the ANSI Z-79.8 Standards were adopted, Ohio Medical Products was engineering a significant development in gas machines. One that would greatly advance anesthesia safety, technology and convenience.

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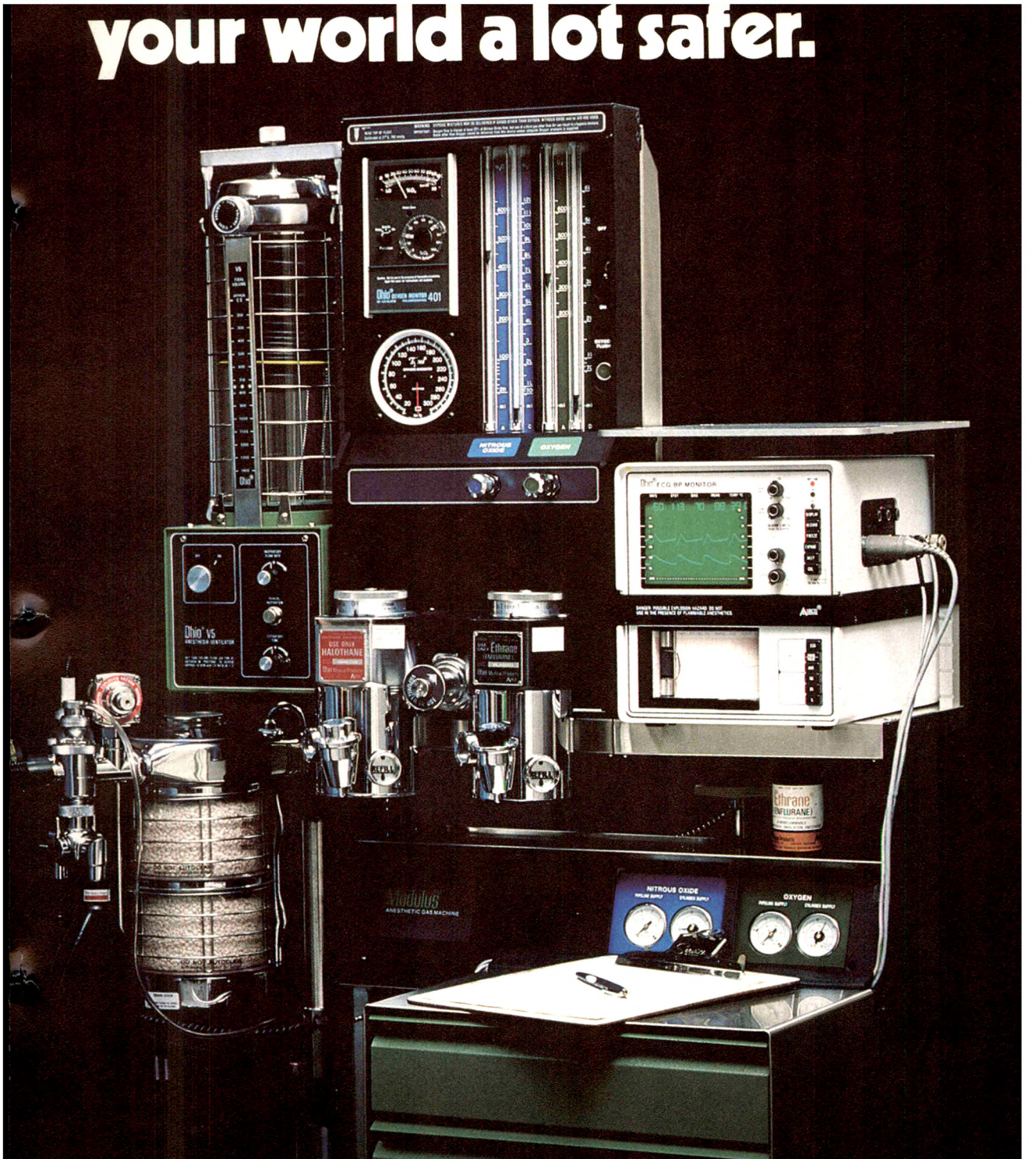
Opens a new generation of safety.

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Anesthetic agent vaporizers are is on the Modulus. A positive vap selector interlock valve allows y select either vaporizer. Or a bypas circuit can be engaged when bo porizers are turned off. What's mo agent circuits are parallel, thus h to prevent accidental mixing with circuitry.

[1]Developed in association with Dr. Patrick Bennett, Group Health Cooperative, Puget Sound, Seattle, Washington

your world a lot safer.



Key components of the Modulus are easily removable for service. Extensive use of pin-indexing and DISS connections helps prevent accidental interchange of similar components. Controls, indicators and work surfaces are located in optimal viewing and operational zones — key factors in your comfort as well as operational safety.

Modularity enhances versatility and convenience.

As its name implies, the Ohio Modulus is totally modular. Key components are removable, so you can order a machine with the configuration to conform to your

You select the gases, vaporizers and flow ranges to meet the needs of your patients. You can order a machine which will accommodate two to four gases and two anesthetic agent vaporizers. You can also have key monitoring and functional controls located where you want them, not where main frame design dictates.

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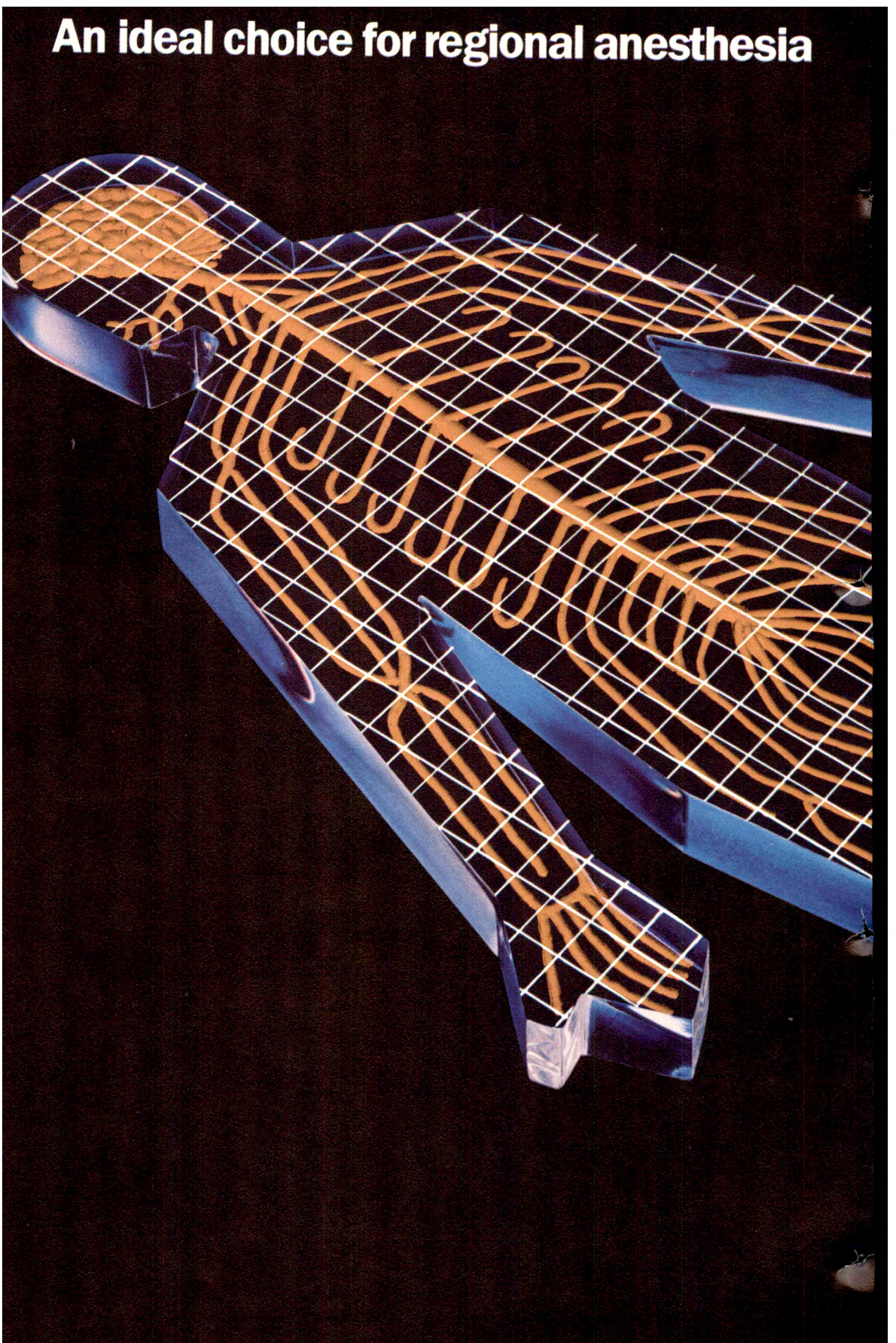
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Nesacaine. An ideal choice for regional anesthesia that has been used effectively and safely in millions of obstetric, surgical, and diagnostic procedures since 1956.



Nesacaine®
(chloroprocaine hydrochloride)

Please turn page for brief summary of prescribing information.

Nesacaine®
(chloroprocaine hydrochloride)

Nesacaine®-CE
(chloroprocaine hydrochloride)

BRIEF SUMMARY:
Nesacaine, in multidose vials with preservative, is indicated for the production of local anesthesia by infiltration and regional nerve block; it should not be used for caudal or epidural anesthesia.

Nesacaine-CE, in single dose vials without preservative, is indicated for the production of local anesthesia by infiltration and regional nerve block, including caudal and epidural blocks.

Contraindications: hypersensitivity to drugs of the PABA ester group; central nervous system disease is a contraindication to caudal or epidural block.

Warnings: RESUSCITATIVE EQUIPMENT AND DRUGS SHOULD BE IMMEDIATELY AVAILABLE WHEN ANY LOCAL ANESTHETIC IS USED.

Usage in Pregnancy: Safe use of chloroprocaine HCl has not been established with respect to adverse effects upon fetal development. This fact should be carefully considered before administering the drug to women of childbearing potential, particularly during early pregnancy.

Obstetrical Paracervical Block: Chloroprocaine is not recommended for obstetrical paracervical block when toxemia of pregnancy is present or when fetal distress or prematurity is anticipated in advance of the block. Fetal bradycardia has been noted by electronic monitoring in about 5-10% of the cases where initial doses of 120 mg to 140 mg of chloroprocaine were used. The incidence of bradycardia, within this dose range, might not be dose related. These data are limited and are generally restricted to non-toxemic cases where fetal distress or prematurity was not anticipated in advance of the block. The role of drug factors and non-drug factors associated with fetal bradycardia following paracervical block are unexplained at this time.

In obstetrics, some oxytocic drugs may cause severe persistent hypertension if vasoconstrictor drugs are used to correct hypotension or are added to the local anesthetic solution.

Solutions containing vasoconstrictors, particularly epinephrine and norepinephrine, should be used with extreme caution in patients receiving MAO inhibitors and tricyclic antidepressants, since severe prolonged hypertension may occur.

Precautions: The safety and effectiveness of chloroprocaine HCl depends upon proper dosage, correct technique, adequate precautions and readiness for emergencies.

Solutions containing vasoconstrictors should be used cautiously in the presence of disease which may adversely affect the patient's cardiovascular system, in areas where the blood supply is limited, or when peripheral vascular disease is present.

Injections should always be made slowly and with frequent aspiration to avoid inadvertent rapid intravascular administration which can produce systemic toxicity.

Serious cardiac arrhythmias may occur if preparations containing a vasopressor are used in patients during or following the administration of chloroform, halothane, cyclopropane, trichlorethylene, or other related agents.

Adverse Reactions: *Systemic adverse reactions* result from high plasma levels due to rapid absorption, inadvertent intravascular injection, excessive dosage, hypersensitivity, idiosyncrasy, or diminished tolerance. *Central nervous system reactions:* excitation and/or depression; restlessness, anxiety, dizziness, blurred vision, or tremors, possibly proceeding to convulsions. Depression may be the first manifestation followed by drowsiness merging into unconsciousness and respiratory arrest.

Cardiovascular system reactions: depression of the myocardium manifested by an initial episode of hypotension, bradycardia, and cardiac arrest.

Neurologic adverse reactions: In the practice of epidural block, occasional inadvertent penetration of the subarachnoid space may occur; subsequent reactions may include spinal block of varying magnitude, loss of bowel and bladder control, loss of perineal sensation and sexual function. Persistent neurological deficit of some lower spinal segments with slow recovery (several months) has been reported in rare instances.

Dosage and Administration: See full prescribing information.

NESACAINE is supplied in 1% and 2% solutions in 30 ml multiple dose vials.

NESACAINE-CE is supplied in 2% and 3% solutions in 30 ml single dose vials.

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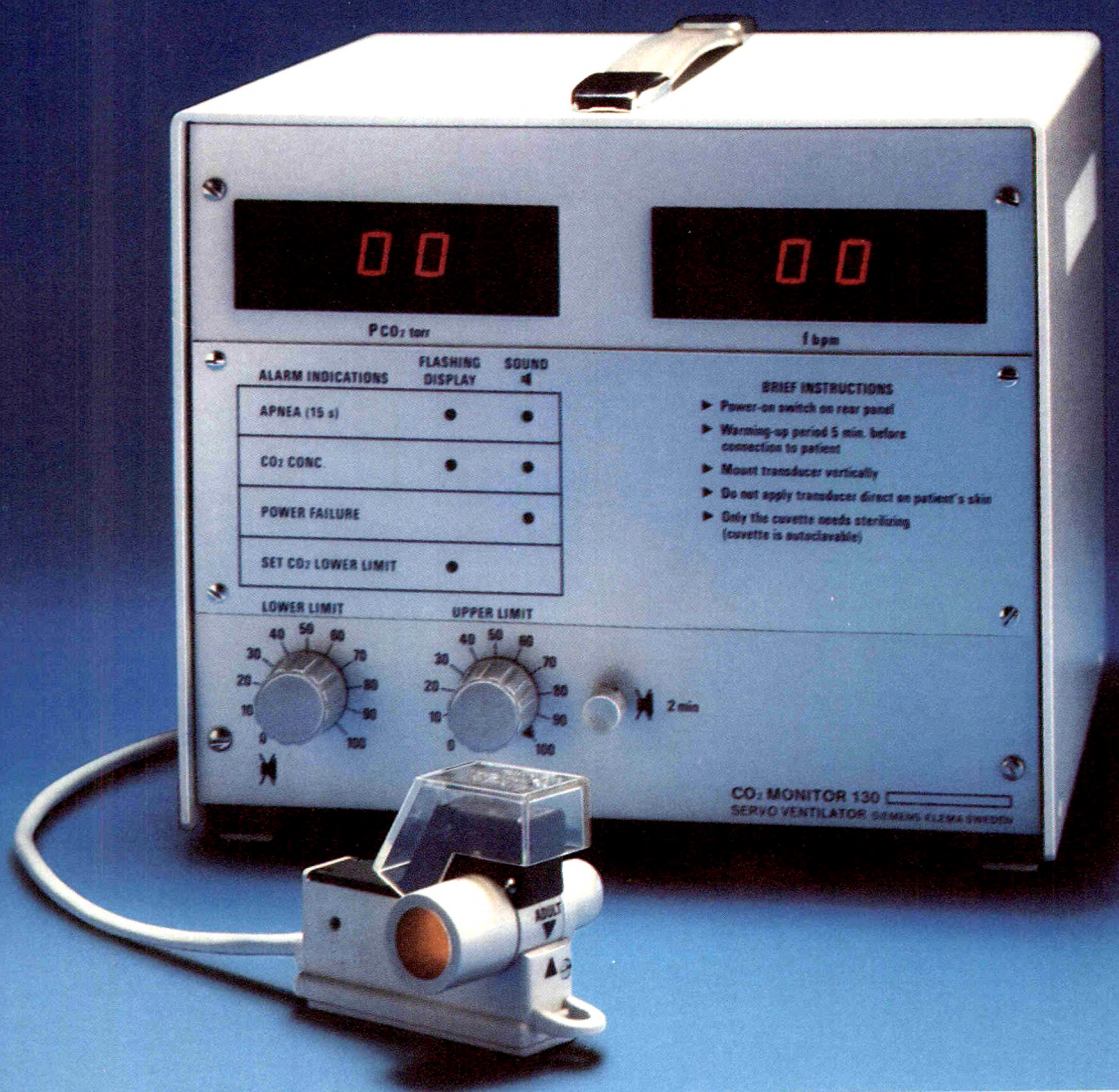
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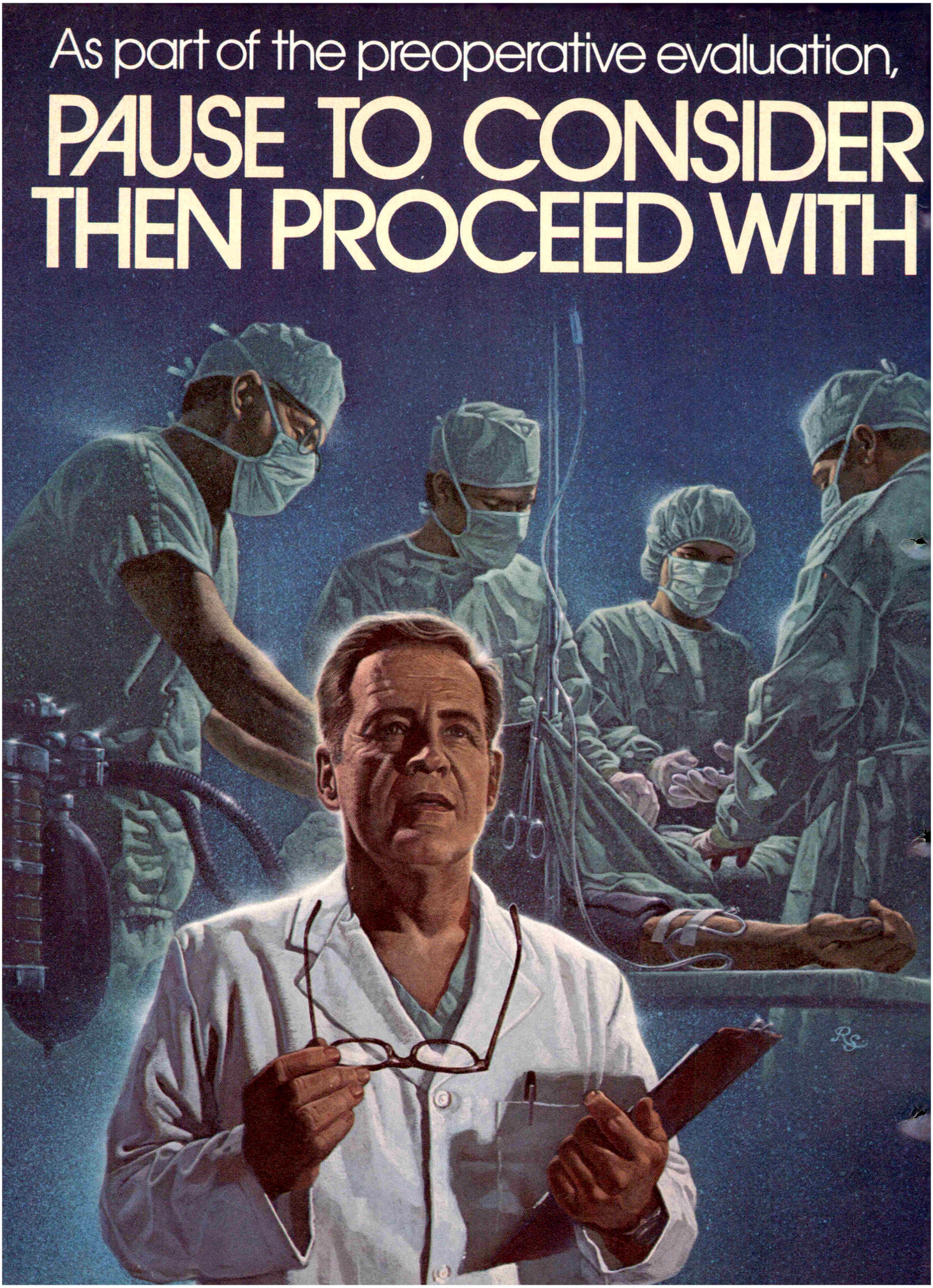
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BRIEF SUMMARY
(Please consult package insert for full prescribing information.)

THIS DRUG SHOULD ONLY BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

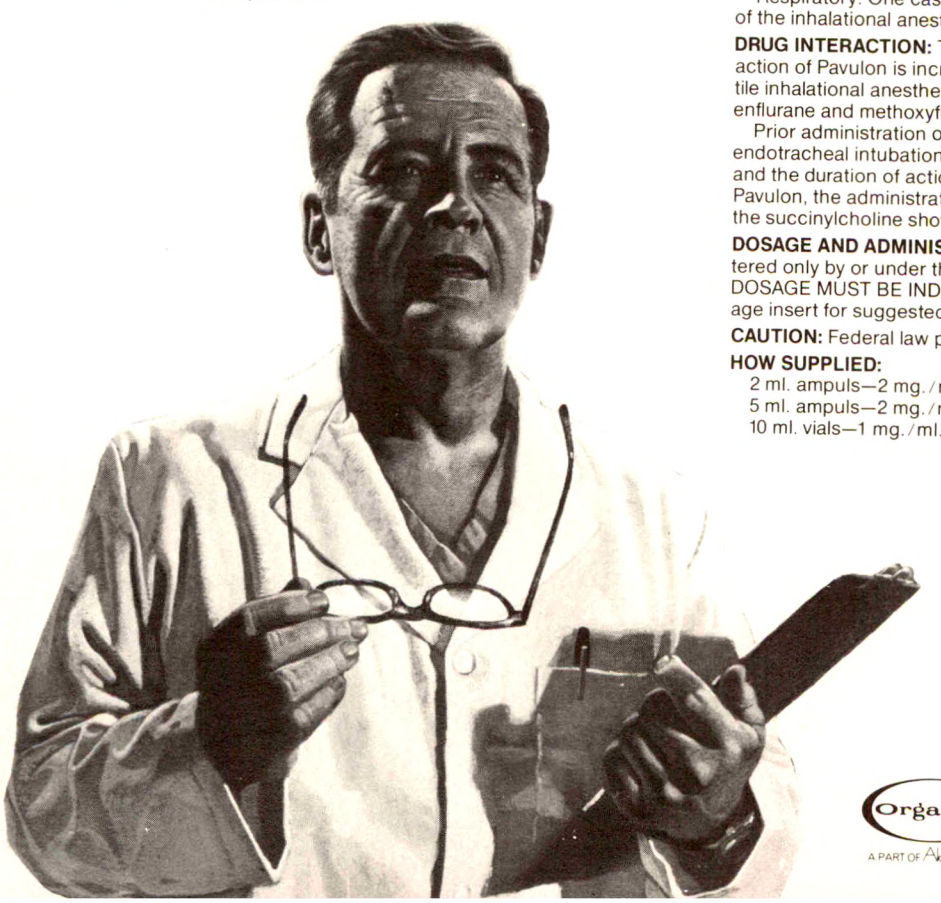
ACTIONS: Pavulon is a non-depolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform) on the myoneural junction.

Pavulon (pancuronium bromide) is antagonized by acetylcholine, anticholinesterases, and potassium ion. Its action is increased by inhalational anesthetics such as halothane, diethyl ether, enflurane and methoxyflurane, as well as quinine, magnesium salts, hypokalemia, some carcinomas, and certain antibiotics such as neomycin, streptomycin, clindamycin, kanamycin, gentamicin and bacitracin. The action of Pavulon may be altered by dehydration, electrolyte imbalance, acid-base imbalance, renal disease, and concomitant administration of other neuromuscular agents.

CONTRAINDICATIONS: Pavulon is contraindicated in patients known to be hypersensitive to the drug or to the bromide ion.

WARNINGS: PAVULON SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS, WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION.

In patients who are known to have myasthenia gravis small doses of Pavulon may have profound effects. A peripheral nerve stimulator is especially valuable in assessing the effects of Pavulon in such patients.



USAGE IN PREGNANCY: The safe use of pancuronium bromide has not been established with respect to the possible adverse effects upon fetal development. Therefore, it should not be used in women of childbearing potential and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the unknown hazards.

Pavulon may be used in operative obstetrics (Cesarean section), but reversal of pancuronium may be unsatisfactory in patients receiving magnesium sulfate for toxemia of pregnancy, because magnesium salts enhance neuromuscular blockade. Dosage should usually be reduced, as indicated, in such cases.

PRECAUTIONS: Although Pavulon has been used successfully in many patients with pre-existing pulmonary, hepatic, or renal disease, caution should be exercised in these situations. This is particularly true of renal disease since a major portion of administered Pavulon is excreted unchanged in the urine.

ADVERSE REACTIONS: Neuromuscular: the most frequently noted adverse reactions consist primarily of an extension of the drug's pharmacological actions beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle relaxation resulting in respiratory insufficiency or apnea. Inadequate reversal of the neuromuscular blockade by anticholinesterase agents has also been observed with Pavulon (pancuronium bromide) as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate.

Cardiovascular: A slight increase in pulse rate is frequently noted.

Gastrointestinal: Salivation is sometimes noted during very light anesthesia, especially if no anticholinergic premedication is used.

Skin: An occasional transient rash is noted accompanying the use of Pavulon.

Respiratory: One case of wheezing, responding to deepening of the inhalational anesthetic, has been reported.

DRUG INTERACTION: The intensity of blockade and duration of action of Pavulon is increased in patients receiving potent volatile inhalational anesthetics such as halothane, diethyl ether, enflurane and methoxyflurane.

Prior administration of succinylcholine, such as that used for endotracheal intubation, enhances the relaxant effect of Pavulon and the duration of action. If succinylcholine is used before Pavulon, the administration of Pavulon should be delayed until the succinylcholine shows signs of wearing off.

DOSAGE AND ADMINISTRATION: Pavulon should be administered only by or under the supervision of experienced clinicians. DOSAGE MUST BE INDIVIDUALIZED IN EACH CASE. See package insert for suggested dosages.

CAUTION: Federal law prohibits dispensing without prescription.

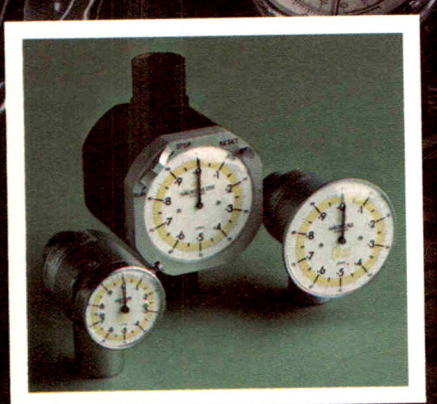
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Please consult full prescribing information before prescribing. A summary follows:

Indications. Peripheral nerve block, infiltration, sympathetic block, caudal, or epidural block.

Contraindication. Marcaine is contraindicated in patients with known hypersensitivity to it.

Warnings. RESUSCITATIVE EQUIPMENT AND DRUGS SHOULD BE READILY AVAILABLE WHEN ANY LOCAL ANESTHETIC IS USED.

Usage in Pregnancy. The relevance to the human is not known. Safe use in pregnant women other than those in labor has not been established.

Until further clinical experience is gained, paracervical block with Marcaine is not recommended. Fetal bradycardia frequently follows paracervical block with some amide-type local anesthetics and may be associated with fetal acidosis. Added risk appears to be present in prematurity, toxemia of pregnancy, and fetal distress.

The obstetrician is warned that severe persistent hypertension may occur after administration of certain oxytocic drugs, if vasopressors have already been used during labor (e.g., in the local anesthetic solution or to correct hypotension).

Solutions containing a vasoconstrictor, particularly epinephrine or norepinephrine, should be used with extreme caution in patients receiving monoamine oxidase (MAO) inhibitors or antidepressants of the triptyline or imipramine types, because severe, prolonged hypertension may result.

Local anesthetics which contain preservatives, i.e., those supplied in multiple dose vials, should not be used for caudal or epidural anesthesia.

Until further experience is gained in children younger than 12 years, administration of Marcaine in this age group is not recommended.

Precautions. The safety and effectiveness of local anesthetics depend upon proper dosage, correct technique, adequate precautions, and readiness for emergencies.

The lowest dosage that gives effective anesthesia should be used in order to avoid high plasma levels and serious systemic side effects. Injection of repeated doses of Marcaine may cause significant increase in blood levels with each additional dose, due to accumulation of the drug or its metabolites or due to slow metabolic degradation. Tolerance varies with the status of the patient. Debilitated, elderly patients and acutely ill patients should be given reduced doses commensurate with age and physical condition.

Solutions containing a vasoconstrictor should be used cautiously in areas with limited blood supply, in the presence of diseases that may adversely affect the patient's cardiovascular system, or in patients with peripheral vascular disease.

Marcaine should be used cautiously in persons with known drug allergies or sensitivities, particularly to the amide-type local anesthetics.

Serious dose-related cardiac arrhythmias may occur if preparations containing a vasoconstrictor such as epinephrine are employed in patients during or following the administration of chloroform, halothane, cyclopropane, trichloroethylene, or other related agents. In deciding whether to use these products concurrently in the same patient, the combined action of both agents upon the myocardium, the concentration and volume of vasoconstrictor used, and the time since injection, when applicable, should be taken into account.

Caution is advised in administration of repeat doses of Marcaine to patients with severe liver disease.

Use in Ophthalmic Surgery. When Marcaine 0.75% is used for retrobulbar block, complete corneal anesthesia usually precedes onset of clinically acceptable external ocular muscle akinesia. Therefore, presence of akinesia rather than anesthesia alone should determine readiness of the patient for surgery.

Adverse Reactions. Reactions to Marcaine are characteristic of those associated with other amide-type local anesthetics. A major cause of adverse reactions to this group of drugs is excessive plasma levels, which may be due to overdosage, inadvertent intravascular injection, or slow metabolic degradation.

Excessive plasma levels of the amide-type local anesthetics cause systemic reactions involving the central nervous system and the cardiovascular system. The *central nervous system effects* are characterized by excitation or depression. The first manifestation may be nervousness, dizziness, blurred vision, or tremors, followed by drowsiness, convulsions, unconsciousness, and possibly respiratory arrest. Since excitement may be transient or absent, the first manifestation may be drowsiness, sometimes merging into unconsciousness and respiratory arrest. Other central nervous system effects may be nausea, vomiting, chills, constriction of the pupils, or tinnitus. The *cardiovascular manifestations* of excessive plasma levels may include depression of the myocardium, blood pressure changes (usually hypotension), and cardiac arrest. In obstetrics, cases of fetal bradycardia have occurred (see Warnings). *Allergic reactions,* which may be due to hypersensitivity, idiosyncrasy, or diminished tolerance, are characterized by cutaneous lesions (e.g., urticaria), edema, and other manifestations of allergy. Detection of sensitivity by skin testing is of doubtful value. Sensitivity to methylparaben preservatives added to multiple dose vials has been reported. Single dose vials without methylparaben are also available.

Reactions following epidural or caudal anesthesia also may include: high or total spinal block; urinary retention; fecal incontinence; loss of perineal sensation and sexual function; persistent analgesia, paresthesia, and paralysis of the lower extremities; headache and backache; and slowing of labor and increased incidence of forceps delivery.

Treatment of Reactions. Toxic effects of local anesthetics require symptomatic treatment; there is no specific cure. The physician should be prepared to maintain an airway and to support ventilation with oxygen and assisted or controlled respiration as required. Supportive treatment of the cardiovascular system includes intravenous fluids and, when appropriate, vasopressors (preferably those that stimulate the myocardium). Convulsions may be controlled with oxygen and intravenous administration, in small increments, of a barbiturate, as follows: preferably, an ultrashort-acting barbiturate such as thiopental or thiamylal; if this is not available, a short-acting barbiturate (e.g., secobarbital or pentobarbital) or diazepam. Intravenous barbiturates or anticonvulsant agents should only be administered by those familiar with their use.

Composition of Solutions.

Marcaine 0.25%—Each ml contains 2.5 mg bupivacaine with NaCl for isotonicity in water for injection.

Marcaine 0.5%—Each ml contains 5 mg bupivacaine with NaCl for isotonicity in water for injection.

Marcaine 0.75%—Each ml contains 7.5 mg bupivacaine with NaCl for isotonicity in water for injection.

In multiple dose vials, each ml also contains 1 mg methylparaben.

In epinephrine, each ml also contains 0.0091 mg epinephrine bitartrate, 0.5 mg sodium bisulfite, 0.001 ml monothioglycerol, 2 mg ascorbic acid, 0.0017 ml 60% sodium lactate, and 0.1 mg edetate calcium disodium.

References:

1. Scanlon JW: Obstetric anesthesia as a neonatal risk factor in normal labor and delivery. *Clinics in Perinatology* 1:465-482, 1974.
2. Scanlon JW, Ostheimer GW, Brown WU, et al: Neurobehavioral responses and drug concentrations in newborns after maternal epidural anesthesia with bupivacaine. *Anesthesiology* 45:400-405, 1976.
3. Ostheimer GW: Obstetrics and local anesthetics: Implications for the fetus and newborn. *Anesthesiology Review* 4:17-23, June 1977.

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ANESTH ANALG
1982;61:75-8

Nitrous Oxide Inactivates Methionine Synthetase in Human Liver

Donald D. Koblin, PhD,* Lucy Waskell, MD, PhD,† Joe E. Watson,‡ E.L.R. Stokstad, PhD,§ and Edmond I. Eger II, MD‖

KOBLIN, D. D., WASKELL, L., WATSON, J. E., STOKSTAD, E.L.R., AND EGER, E. I., II: Nitrous oxide inactivates methionine synthetase in human liver. Anesth Analg 1982;61:75-8.

Activity of methionine synthetase was measured in liver biopsies of seven patients who had received 50% to 70% nitrous oxide supplemented by a combination of a narcotic and/or barbiturate with or without a volatile anesthetic, and from seven patients who were anesthetized without nitrous oxide (control group). Methionine synthetase activity (±SE) averaged 219 ± 28 nmol of methionine per hour per gram of liver in patients given nitrous oxide, and 414 ± 29 in control patients. Inactivation of methionine synthetase progressively increased as the product of the concentration of nitrous oxide and the exposure time increased. These results in humans are similar to those in animals and suggest that inactivation of methionine synthetase may play a role in the development of the pathologic effects seen in patients and medical personnel after exposure to nitrous oxide.

Key Words: ANESTHETICS, Gases: nitrous oxide; LIVER: enzymes, methionine synthetase; ENZYMES: methionine synthetase.

IN RATS (1-5) and mice (6), exposure to nitrous oxide markedly decreases the activity of methionine synthetase in liver and brain. Methionine synthetase is a vitamin B_{12}-dependent enzyme that catalyzes the transfer of a methyl group from N^5-methyltetrahydrofolate to homocysteine to form methionine and tetrahydrofolate. Nitrous oxide may inhibit methionine synthetase by oxidizing the cobalt atom of the coenzyme from its active Co(I) oxidation state (7). The nitrous oxide-induced depression in methionine synthetase activity is associated with an impairment in DNA synthesis (8-10). Inactivation of methionine synthetase may be related to the increase in hepatic, renal, and neurologic disease seen in patients and medical personnel after prolonged exposure to subanesthetic and trace levels of nitrous oxide (11, 12).

Despite numerous reports of nitrous oxide-induced inactivation of methionine synthetase in animals, tissues from humans exposed to nitrous oxide have not been examined. Such experiments are needed because of marked differences in the physiologic effects of vitamin B_{12} deficiency between humans and animals. For example, both neurologic symptoms and megaloblastic anemia occur in humans who have a vitamin B_{12} deficiency. In contrast, no hematologic abnormalities are observed in vitamin B_{12}-deficient animals, e.g., rhesus monkeys or baboons fed a diet depleted of cobalamin for more than 4 years (13). Because of possible differences in inactivation of vitamin B_{12} between humans and animals, we determined the ability of nitrous oxide to decrease methionine synthetase activity in liver biopsies from patients undergoing surgical procedures.

Methods

Liver biopsies were obtained from 14 patients

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Supported in part by National Institutes of Health research grants GM 15571, GM 27791, and AM 08171; the Anesthesia Research Foundation; the Norris Foundation; and the University of California, San Francisco Academic Senate Committee on Research.
Received from the Departments of Anesthesia, University of California, San Francisco and Veterans Administration Medical Center, San Francisco, and the Department of Nutritional Sciences, University of California, Berkeley, California. Accepted for publication September 26, 1981.

Reprint requests to Dr. Eger, Department of Anesthesia, University of California, HSE 1386, Third and Parnassus Avenues, San Francisco, CA 94143.

(A.S.A. class II to III) undergoing abdominal surgery for therapeutic or diagnostic reasons. Approval was received from the University Committee on Human Research, and informed consent was obtained from each of the patients. Seven patients (mean age 60 ± 4 (SE) years) were given 50% to 70% nitrous oxide supplemented by a combination of barbiturate and/or narcotic with or without a volatile anesthetic (Table). Seven other patients (mean age, 55 ± 5 (SE) years) were anesthetized without nitrous oxide (control group). Duration of anesthesia before biopsy of the liver ranged from 60 to 165 minutes. There was one woman in the control group; the other 13 patients were men.

Sections of liver weighing 0.5 to 1.0 g were removed, immediately frozen on dry ice, and stored at −80 C until analyzed. Methionine synthetase was assayed as described in earlier reports (6, 14). Activity is expressed as nanomoles of methionine produced per hour per gram of liver.

Results

Methionine synthetase activity ranged from 110 to 302 nmol of methionine per hour per gram of liver in patients exposed to nitrous oxide, and from 285 to 523 nmol of methionine per hour per gram of liver in patients not exposed to nitrous oxide (Table). The mean activity was 219 ± 28 (SE) nmol in patients receiving nitrous oxide and 414 ± 29 in the control group ($p < 0.001$).

As patients in the experimental group received different concentrations of nitrous oxide for varying time periods, the results were normalized by relating the activity of methionine synthetase to the total amounts of nitrous oxide administered. The total amount of nitrous oxide administered is represented by the product of the concentration of nitrous oxide in atmospheres and the time period of exposure in hours. Inactivation of methionine synthetase progressively increased with the total amount of nitrous oxide administered (Figure).

Discussion

In the present experiments, we demonstrate that the activity of methionine synthetase in liver is depressed in patients anesthetized with nitrous oxide compared with those anesthetized without nitrous oxide. The absolute values for methionine synthetase activity in human liver after anesthesia are within the range observed in rat (15) and mouse (6) livers. Although the effects of anesthesia per se on methionine synthetase activity in human liver are not known, inhaled anesthetics other than nitrous oxide (isoflurane, enflurane, halothane, xenon) do not affect methionine synthetase activity in livers from mice (6).

The depressed levels of methionine synthetase activity in patients receiving nitrous oxide were not caused by liver disease. Liver biopsies obtained from these patients appeared normal on gross examination and also exhibited normal liver histology by light microscopy. Liver biopsies obtained from patients not exposed to nitrous oxide also appeared normal on gross examination, although light microscopy re-

TABLE

Methionine Synthetase Activity in Liver Biopsies of Patients Undergoing Operative Procedures with Various Anesthetics with and without Nitrous Oxide

Patient no.	Operation	Anesthetic	N_2O	Duration of anesthesia before biopsy	Methionine synthetase activity
			%	*hr*	$nmol \cdot hr^{-1} \cdot g^{-1}$
1	Cholecystectomy	Thiamylal, isoflurane, N_2O	60	2.08	149
2	Cholecystectomy	Morphine, N_2O	66	2.75	110
3	Cholelithotomy	Thiamylal, N_2O	60	1.25	282
4	Colectomy	Enflurane, lidocaine epidural, N_2O	50	2.75	178
5	Lysis of adhesions	Thiamylal, enflurane, N_2O	60	1.58	265
6	Gastrojejunostomy	Morphine, thiamylal, N_2O	70	2.00	302
7	Colectomy	Fentanyl, N_2O	60	1.75	246
8	Colectomy	Thiamylal, isoflurane	0	2.75	486
9	Cholecystectomy	Isoflurane	0	1.5	428
10	Gastrojejunostomy	Thiamylal, isoflurane	0	2.0	378
11	Lysis of adhesions	Thiamylal, enflurane	0	1.5	523
12	Gastrostomy	Thiamylal, enflurane	0	1.0	395
13	Hemigastrectomy	Thiamylal, enflurane	0	1.0	285
14	Cholecystectomy	Thiamylal, enflurane, lidocaine epidural	0	1.5	401

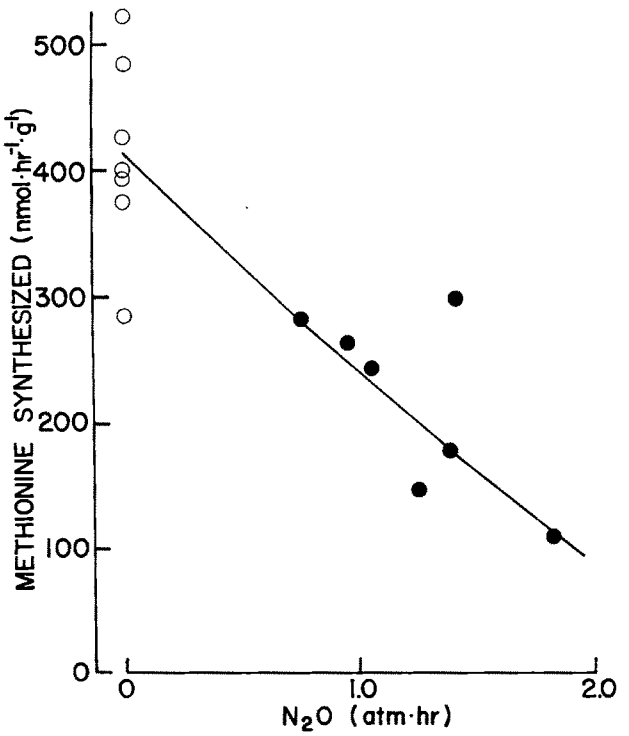


FIGURE. Methionine synthetase activity is plotted against product of nitrous oxide concentration and period of exposure (i.e., total exposure of nitrous oxide administered), expressed in terms of atmospheres per hour. Open circles represent levels of activity in liver of patients not exposed to nitrous oxide; solid circles represent levels of activity in patients who were exposed to nitrous oxide at concentrations of 50% to 70% for 1.25 to 2.75 hours. Curve begins at average level of methionine synthetase activity in control patients, 414 nmol of methionine per hour per gram of liver.

vealed a moderate fatty metamorphosis in one of the specimens.

It should be noted that the patients in this study were not receiving thyroid drugs nor did they have thyroid abnormalities. This may be important because the feeding of thyroid powder to rats increases vitamin B_{12} requirement, and thyroidectomy produces approximately a 2-fold increase in the hepatic levels of methionine synthetase (15).

The greatest depression in enzyme activity was observed in the patient who was exposed to 66% nitrous oxide for 2.75 hours (Table); it was approximately 25% of the mean control value. Whether a more prolonged exposure to nitrous oxide would have caused a further inactivation remains to be investigated. There are quantitative differences concerning the maximal extent of enzyme inactivation in rats. Deacon et al (16) reported that exposure of rats to 50% nitrous oxide for 6 hours decreased methionine synthetase to 1% of control values. However, other investigators have found that exposure of rat hepatocytes to 80% nitrous oxide for 20 to 24 hours decreased methionine synthetase activity to 10% to 14% of control values (2). Also, 2 days' exposure of rats to 50% nitrous oxide has been reported to decrease activity to 27% of the control value (4). We found that methionine synthetase activity in mice decreased to 5% to 25% of the original value after exposure to 0.8 atm of nitrous oxide for 4 hours, and that the magnitude of the depression varied among groups of animals (6).

Perhaps more important and more difficult to measure in humans is the time of recovery of enzyme activity following nitrous oxide exposure. After mice are exposed to 0.8 atm of nitrous oxide for 4 hours, enzyme activity returns to 70% of control levels within 1 day and is not significantly different from control levels within 2 days (6). In rats exposed to 50% nitrous oxide for 15 hours, enzyme activity reaches 70% of normal within 2 days (4) and activity may be depressed for as long as 4 days (1, 4). The inactivation of methionine synthetase may potentially impair DNA and protein synthesis. If recovery from inactivation of methionine synthetase occurs slowly in humans, deleterious effects may arise from even short exposures to nitrous oxide.

ACKNOWLEDGMENTS

We thank Drs. L. Way, C. Pellegrini, R. Williams, G. Zsigmond, and J. Harwood and their surgical residents for obtaining the liver biopsies.

REFERENCES

1. Deacon R, Lumb M, Perry J, et al. Inactivation of methionine synthetase by nitrous oxide. Eur J Biochem 1980;104:419–22.
2. Horne DW, Briggs WT. Effect of dietary and nitrous oxide-induced vitamin B-12 deficiency on uptake of 5-methyltetrahydrofolate by isolated rat hepatocytes. J Nutr 1980;110:223–30.
3. Suleiman SA, Spector R. Methionine synthetase in mammalian brain: function development and distribution. Life Sci 1980;27:2427–32.
4. Kondo H, Osborne ML, Kolhouse JF, et al. Nitrous oxide has multiple deleterious effects on cobalamin metabolism and causes decreases in the activities of both mammalian cobalamin-dependent enzymes in rats. J Clin Invest 1981;67:1270–83.
5. Chanarin I. Cobalamins and nitrous oxide: a review. J Clin Pathol 1980;33:909–16.
6. Koblin DD, Watson JE, Deady JE, Stokstad ELR, Eger EI II. Inactivation of methionine synthetase by nitrous oxide in mice. Anesthesiology 1981;54:318–24.
7. Blackburn R, Kyaw M, Swallow AJ: Reaction of Cob(I)alamin with nitrous oxide and Cob(III)alamin. J Chem Soc Faraday Trans 1977;73:250–5.
8. Amess JAL, Rees GM, Burman JF, Nancekievill DG, Mollin DL. Megaloblastic haemopoiesis in patients receiving nitrous oxide. Lancet 1978;1:339–42.

9. McKenna B, Weir DG, Scott JM. The induction of functional vitamin B-12 deficiency in rats by exposure to nitrous oxide. Biochim Biophys Acta 1980;628:314–21.
10. Cupiola RR, Beckert WH. The suppression of population, mitotic index and ^{3}H-thymidine incorporation in cultured mouse fibroblasts in response to nitrous oxide. Res Commun Substance Abuse 1980;1:427–41.
11. Layzer RB. Myeloneuropathy after prolonged exposure to nitrous oxide. Lancet 1978;2:1227–30.
12. Cohen EN, Brown BW, Wu ML, et al. Occupational disease in dentistry and chronic exposure to trace anesthetic gases. J Am Dent Assoc 1980;101:21–31.
13. England JM, Linnell JC. Haematological aspects of cobalamin deficiency. In: Zagalak B, Friedrich W, eds. Vitamin B_{12}. New York: Walter de Gruyter, 1979:991–1000.
14. Sauer HJ, Jaenicke L. Einfacher Test zur Messung der Methionin-Synthetase-(MS-) Activität und seine Anwendungsmöglichkeiten in der Klinik. Klin Wochenschr 1972;50:986–90.
15. Stokstad ELR, Chan MS, Watson JE, Brody T, Jaenicke L. The effect of hypothyroidism on histidine oxidation and folate-dependent enzyme levels. In: Zagalak B, Friedrich W, eds. Vitamin B_{12}. New York: Walter de Gruyter, 1979:1139–44.
16. Deacon R, Lumb M, Perry J, et al. Selective inactivation of vitamin B12 in rats by nitrous oxide. Lancet 1978;2:1023–4.

Use of Isoproterenol in Primary Pulmonary Artery Hypertension

The experience derived from the administration of isoproterenol in six patients with pulmonary hypertension of unknown etiology (PAH-UE) is presented. The diagnosis was made after exclusion of other known diseases capable of producing hypertension in the pulmonary circulation. Catheterization was performed, and basal cardiopulmonary parameters, mean pulmonary artery pressure (PAP), pulmonary arteriolar resistance (PAR), cardiac index (CI), alveolar-arterial oxygen tension difference $P(A\text{-}a)O_2$, and Pa_{O_2} were investigated. The effect of infusing 3 μg/min of isoproterenol into the pulmonary artery was studied in five patients. Isoproterenol was given sublingually to one patient who had previously received it intravenously; in another patient it was given only sublingually. Significant changes ($p < 0.05$) were noted in heart rate, CI, PAR, and mean PAP after administration of isoproterenol. A favorable effect on the heart and lungs was seen in two patients, and this was maintained for three years with sublingual isoproterenol with a favorable cardiorespiratory effect. Use of isoproterenol in PAH-UE is justified at present in those cases with a favorable cardiopulmonary response as no specific therapy is available. (*Lupi-Herrera E, Bialostozky D, Sobrino A: The role of isoproterenol in pulmonary artery hypertension of unknown etiology (primary): Short- and long-term evaluation. Chest 1981;79:292–6*)

ANESTH ANALG
1982;61:79-82

Postanesthetic Hepatic Injury in Rats: Influence of Alterations in Hepatic Blood Flow, Surgery, and Anesthesia Time

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HARPER, M. H., COLLINS, P., JOHNSON, B. H., EGER, E. I., II, AND BIAVA, C. G.: Postanesthetic hepatic injury in rats: influence of alterations in hepatic blood flow, surgery, and anesthesia time. Anesth Analg 1982;61:79-82.

Hepatic injury was measured in enzyme-induced rats following ligation of the hepatic artery performed under anesthesia with thiamylal, halothane, enflurane, or isoflurane. The influence of surgical site was determined by performing upper abdominal (sham ligation), lower abdominal, and peripheral surgery on rats anesthetized with halothane. The effect of anesthesia time was evaluated by continuing halothane anesthesia for 1, 2, or 4 hours after upper abdominal (sham ligation) surgery. Centrilobular necrosis did not occur in enzyme-induced rats anesthetized with thiamylal, isoflurane, or enflurane, or in halothane-anesthetized animals that had not undergone enzyme induction. When halothane was the anesthetic, hepatic injury was significant after both the sham operation and ligation of the hepatic artery, and hepatic injury was directly related to anesthesia time. Lower abdominal surgery and the sham operation were associated with comparable hepatic damage, which was more than that occurring after peripheral surgery.

Key Words: ANESTHETICS, Volatile: enflurane, halothane, isoflurane; BIOTRANSFORMATION: enzyme induction; LIVER: blood flow, hepatotoxicity.

THE HYPOXIC model for halothane-induced liver injury has been well characterized. Induction of hepatic biotransformation enzyme systems and a reduced F_{IO_2} are the factors necessary to produce halothane hepatotoxicity in animals (1, 2). The metabolism of halothane under hypoxic conditions is thought to proceed along a reductive pathway which results in the formation of reactive intermediates. These intermediates may cause injury by covalently binding to hepatic macromolecules (3).

This model suggests that enzyme induction may predispose patients to hepatic injury if they become hypoxic during halothane anesthesia. Drug therapy, premedicants, and environmental pollutants are potent inducers of hepatic enzymes, and thus might lead to injury if halothane and hypoxia are subsequently imposed. Because inspired and arterial oxygen levels are monitored and controlled, hypoxemia rarely occurs or persists during clinical anesthesia. However, another mechanism may lead to hepatic hypoxia and reductive metabolism of halothane. Hepatic parenchymal oxygen levels can be lowered by decreasing hepatic blood flow. In patients anesthetized with halothane, upper abdominal surgery may decrease this flow and thereby produce hepatic injury (4).

To test this thesis, we measured hepatic injury in enzyme-induced rats following ligation of the hepatic artery performed under thiamylal, halothane, enflurane, or isoflurane anesthesia. The relative contributions of enzyme induction, surgical manipulation without ligation, surgical site, and anesthesia time were determined by performing a sham operation in the area of the hepatic artery with and without enzyme induction, by performing lower abdominal and peripheral surgery, and by increasing the duration of

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Supported in part by National Institutes of Health Anesthesia Research Center Grant GM 15571 and the Anesthesia Research Foundation.

Received from the Department of Anesthesia, University of California, San Francisco, California. Accepted for publication September 30, 1981. Presented in part at the 55th Congress of the International Anesthesia Research Society, March 8-12, 1981, Atlanta, Georgia.

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anesthesia from 15 minutes to 1, 2, and 4 hours in animals anesthetized with halothane.

Methods

Two hundered thirteen adult male Sprague-Dawley rats (Charles River), weighing approximately 200 g each, received Purina Laboratory Chow ad libitum. Animals undergoing enzyme induction received phenobarbital (1 mg/ml) in their drinking water for 4 days, but not for the 24 hours preceding each study. We eliminated from the study any animal consuming less than 16 mg/day, and all other animals had a daily phenobarbital solution intake of 16 to 39 mg.

We anesthetized the rats in individual plastic chambers. Oxygen delivered via Matheson 603 and 602 flowmeters at a rate of 5 L/min to calibrated vaporizers permitted administration of halothane (1%), enflurane (2%), or isoflurane (1.4%). Anesthetic concentrations in the chambers were determined using gas chromatography. For surgery, anesthesia was delivered via a plastic mask having an opening lined with rubber that fit around the head and ears. Heat lamps maintained rectal temperature between 37.0 and 38.5 C. Rats were killed with 100% CO_2 24 hours after anesthesia and their livers removed for microscopic examination. Using light microscopy, a pathologist (C.G.B.) examined the sections for evidence of damage. We graded hepatic injury in a blind manner according to the criteria of McLain et al (1): 0, normal, no pathologic changes; 1, slight cellular disruption; 2, some staining variations and occasional appearance of vacuoles or balloon cells; 3, occasional centrilobular necrosis; 4, many centrilobular necrotic areas; 5, confluent centrilobular necrosis.

Surgery consisted of the following procedures: Ligation of the hepatic artery was performed through a 3-cm incision in the upper abdomen. A Zeiss OPMI-1 operating microscope facilitated identification and dissection of structures. The hepatic artery was exposed and ligated with a 3-0 silk suture. The upper abdominal operation was similar, except that the hepatic artery was not ligated. Lower abdominal surgery consisted of a 3-cm incision above the bladder and exposure of the distal abdominal aorta. For peripheral surgery, a groin incision was made to allow exposure and dissection of the femoral artery and vein. Operating time was 15 to 20 minutes for all animals.

In enzyme-induced rats, the hepatic artery was ligated while the animals were anesthetized with the following anesthetic agents: group I (n = 6), thiamylal, 1.9 mg/kg IM; group II (n = 20), halothane 1%; group III (n = 12), enflurane 2%; group IV (n = 12), isoflurane 1.4%. In groups II to IV, anesthesia was delivered in 100% oxygen and maintained for 2 hours after ligation. Group I (thiamylal) received 100% oxygen during surgery and for 2 hours thereafter. A control group of peer animals underwent enzyme-induction but not surgery or anesthesia.

Groups V to VII were enzyme induced and received halothane anesthesia for surgery [V (n = 24), upper abdominal; VI (n = 12), lower abdominal; and VII (n = 11), peripheral] and for 2 hours thereafter.

Length of anesthesia was varied for groups VIII to X. Animals were enzyme induced, anesthetized with halothane, and had the sham operation. Anesthesia was given as follows: group VIII (n = 11), during surgery only; group IX (n = 12), for 1 hour after surgery; and group X (n = 11), for 4 hours after surgery.

Ligation of the hepatic artery and the sham operation were performed in an additional two groups of rats (group XI, n = 10; and group XII, n = 12) anesthetized with halothane but without enzyme induction.

One-way analysis of variance and standardized rank comparison tests were used to compare differences between groups. Regression analysis was used to determine the increase in damage occurring as a result of longer administration of halothane.

Results

Ligation of the hepatic artery (group II) resulted in significant hepatic injury when the anesthetic agent was halothane (Table 1). The histologic score for halothane was significantly different from that of all other agents and from control values ($p < 0.001$). The scores for thiamylal (group I), enflurane (group III), and isoflurane (group IV) were not significantly different from those in nonanesthetized enzyme-induced control rats.

The hepatic injury score was significantly less after peripheral surgery with halothane (group VII) than after ligation of the hepatic artery (group II), upper abdominal (group V), or lower abdominal surgery (group VII) ($p < 0.001$) (Table 2). Ligation (group II) produced more injury than the upper abdominal (group V) operation ($p < 0.001$). Injury after lower abdominal surgery (group VI) was not significantly different from that after ligation of the hepatic artery (group II) or the upper abdominal operation (group V).

The degree of hepatic injury after an upper abdom-

inal operation with halothane and enzyme induction increased with length of anesthesia (Figure) ($p < 0.001$, $r = 0.4$, groups VIII to X).

Hepatic injury occurred only in animals undergoing enzyme induction.

Discussion

We demonstrated that interrupting arterial flow to the liver results in histologic injury in enzyme-induced rats anesthetized with halothane but not thiamylal, enflurane, or isoflurane. Injury is comparable to that found in the original halothane hypoxic model (1). This finding supports the thesis that diminished flow can produce regional hypoxia sufficient to promote reductive metabolism. The absence of hepatic damage with thiamylal, enflurane, and isoflurane is probably due to minimal metabolism of enflurane (5) and isoflurane (6), and perhaps to an absence of reductive metabolic pathways for these agents.

Upper abdominal surgery (sham operation) caused a degree of centrilobular necrosis similar to that found with ligation of the hepatic artery. The amount of injury was directly related to the proximity of surgical trauma to the hepatic blood supply. A positive correlation between total anesthesia time and degree of cellular damage was also established. Histologic scores more than doubled when halothane anesthesia time increased from 15 minutes to 4 hours after upper abdominal surgery.

TABLE 1

Effect of Ligation of Hepatic Artery on Hepatic Injury during Anesthesia with Thiamylal, Halothane, Enflurane, or Isoflurane

Group	n	Anesthetic	Histologic score*
I	6	Thiamylal	0.33 ± 0.3
II	20	Halothane	3.83 ± 0.2
III	12	Enflurane	0.71 ± 0.4
IV	12	Isoflurane	0.33 ± 0.2
Control	20	None	0.20 ± 0.1

* Values are means ± SE. Scores are based on a scale of 0 (no injury) to 5 (confluent centrilobular necrosis).

TABLE 2

Effect of Operative Site on Hepatic Injury during Halothane Anesthesia

Group	n	Operative site	Histologic score*
V	24	Upper abdomen	2.65 ± 0.3
VI	12	Lower abdomen	3.38 ± 0.4
VII	1	Peripheral	2.23 ± 0.4

* Values are means ± SE. Scores are based on a scale of 0 (no injury) to 5 (confluent centrilobular necrosis).

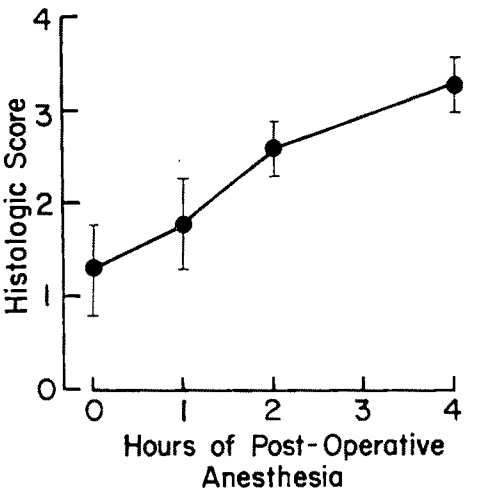


FIGURE. Histologic evidence of hepatic injury increased as duration of halothane anesthesia was prolonged after upper abdominal surgery.

Previous reports have suggested an association between surgery, hepatic blood flow, and hepatic injury. Postoperative elevation of transaminase was reported in one patient who had radiographic evidence of diminished hepatic arterial blood flow during halothane anesthesia (7). Hepatic blood flow has been shown to decrease during surgery, the amount of decrease being related to the oeprative site. Upper abdominal surgery caused a 34% greater decrease in hepatic blood flow than peripheral surgery during halothane anesthesia (4).

Two features of the lesion developed in the rat hypoxic model suggest that it may be similar to that found in man. First, the morphologic findings are strikingly similar. The appearance of swollen hepatocytes and vacuoles with confinement of damage to the centrilobular region occurs in both rats and man. The lesion that develops in the rat hypoxic model closely resembles the microscopic findings observed in human hepatitis due to a variety of causes (8). Second, identical reductive metabolites have been recovered in both animals and man during normoxic anesthesia. In the model, production of these metabolites is markedly increased when enzyme induction, halothane, and hypoxia are combined. It is likely that large amounts of metabolic products must be formed before injury occurs, and that conditions that simulate enzyme induction and hypoxia must coexist to produce clinically apparent halothane hepatotoxicity.

Our findings suggest that patients receiving enzyme-inducing drugs may be at risk of developing postoperative hepatic injury if they receive halothane for lengthy abdominal procedures. This risk decreases

greatly when the surgery is peripheral or when other anesthetics are used.

We have demonstrated that hepatotoxicity can occur in rats when hepatic arterial blood flow is decreased during halothane anesthesia. Abdominal surgery and longer anesthesia times were also associated with severe hepatic injury. Histologic findings were similar in type and degree to those produced by lowering inspired oxygen levels in the rat model.

REFERENCES

1. McLain GE, Sipes IG, Brown BR Jr. An animal model of halothane hepatoxocity: roles of enzyme induction and hypoxia. Anesthesiology 1979;51:321–6.
2. Ross WT Jr, Daggy BP, Cardell RR Jr. Hepatic necrosis caused by halothane and hypoxia in phenobarbital-treated rats. Anesthesiology 1979;51:327–33.
3. Sipes IG, Podolsky TL, Brown BR Jr. Bioactivation and covalent binding of halothane to liver macromolecules. Environ Health Perspect 1977;21:171–8.
4. Gelman SI. Disturbances in hepatic blood flow during anesthesia and surgery. Arch Surg 1976;111:881–3.
5. Chase RE, Holaday DA, Fiserova-Bergerova V, Saidman LJ, Mack FE. The biotransformation of Ethrane in man. Anesthesiology 1971;35:262–7.
6. Holaday DA, Fiserova-Bergerova V, Latto IP, Zumbiel MA. Resistance of isoflurane to biotransformation in man. Anesthesiology 1975;43:325–32.
7. Benumof JL, Bookstein JJ, Saidman LJ, Harris R. Diminished hepatic arterial flow during halothane administration. Anesthesiology 1976;45:545–51.
8. Wills EJ, Walton B. A morphologic study of unexplained hepatitis following halothane anesthesia. Am J Pathol 1978;91: 11–32.

Antibiotic Reversal of Digoxin Activation by Gut Flora

In approximately 10% of patients given digoxin, substantial conversion of the drug to cardioinactive, reduced metabolites (digoxin reduction products, or DRPs) occurs. The site and clinical importance of this conversion is unknown. In four healthy volunteers taking digoxin daily for 4 weeks, urinary excretion of DRPs was greatest after a poorly absorbed tablet was ingested, and least after intravenous administration. Stool cultures from subjects known to make DRPs in vivo ("excretors") converted digoxin to DRPs; cultures from nonexcretors did not. Three excretors were given digoxin tablets for 22 to 29 days. A 5-day course of erythromycin or tetracycline, administered after a base-line period of 10 to 17 days, markedly reduced or eliminated DRP excretion in urine and stool. Serum digoxin concentrations rose as much as 2-fold after antibiotics were given. The authors conclude that in some persons digoxin is inactivated by gastrointestinal bacteria. Changes in the enteric flora may markedly alter the state of digitalization. (*Lindenbaum J, Rund DG, Butler VP Jr, Tse-Eng D, Saha JR: Inactivation of digoxin by the gut flora: reversal by antibiotic therapy. N Engl J Med 1981;305:789–94*)

ANESTH ANALG
1982;61:83-6

Succinylcholine-Induced Hyperkalemia in the Rat following Radiation Injury to Muscle

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CAIROLI, V. J., IVANKOVICH, A. D., VUCICEVIC, D., AND PATEL, K.: Succinylcholine-induced hyperkalemia in the rat following radiation injury to muscle. Anesth Analg 1982;61:83-6.

During anesthetic preparation of a patient who had received routine radiation therapy for sarcoma of the leg, cardiac collapse occurred following succinylcholine (SCh) administration. Experiments were designed to test the hypothesis that radiation injury to muscle might cause increased sensitivity to SCh similar to that reported in patients with muscle trauma, severe burns, and lesions causing muscle denervation. Venous plasma potassium levels and arterial blood gas tensions were measured in rats after they were given SCh (3 mg/kg) at various times following ^{60}Co irradiation of the hind legs. Nonirradiated rats responded to SCh with a slight but statistically significant increase in plasma K^+. Rats subjected to high levels of radiation (10,000 to 20,000 R) and given SCh 4 to 7 days later responded in the same way as the control rats. Plasma K^+ levels in rats exposed to a fractionated irradiated dosage (2500 R given twice with a 1-week interval) followed by SCh 1 week later were similar to those in the control group, but when SCh was given 2 weeks later (3 weeks after initial irradiation) there was a marked elevation of plasma K^+, from 3.6 to 7.7 meq/L, a statistically significant increase.

Key Words: NEUROMUSCULAR RELAXANTS: succinylcholine; IONS: potassium; COMPLICATIONS: radiation.

THIS STUDY was stimulated by a clinical observation involving an otherwise healthy 65-kg teenage patient who had been receiving radiation therapy for a sarcoma in one leg. Before surgery, anesthetic preparation of the patient proceeded routinely until succinylcholine (SCh), 100 mg, was administered to facilitate tracheal intubation. Cardiac collapse immediately occurred and resuscitation was unsuccessful. Numerous reports (1-5) have implicated SCh-induced hyperkalemia as the cause of cardiac arrhythmias and arrest in patients with burns, massive trauma, and such neurologic disorders as spinal cord injuries, lower motor lesions, and muscular dystrophy.

The present study was designed to determine whether in experimental animals, radiation injury to muscle might similarly trigger the development of increased sensitivity fo SCh with resultant hyperkalemia.

Methods

Male Sprague-Dawley rats, each weighing 500 g or more, were sedated with a fentanyl-droperidol mixture (Innovar), 0.4 ml/kg, and taped on lead bricks (8x4x2 inches) in such a way that their hind legs were exposed to ^{60}Co radiation while most of their body was outside the beam path or was protected by lead shielding. Two rats at a time were positioned in this manner 30 cm from the ^{60}Co source, where the air dosage rate was 526 R/min. Animals were assigned to four treatment schedules. Rats in group I received no radiation before the SCh experiment. Those in group II received a high level of radiation (10,000 or 20,000 R) to their legs, followed by SCh on the 4th to 7th postirradiation days. Rats in group III were given a fractional radiation dosage (2500 R on day 0, 2500 R on day 7) followed by SCh on day 14. Group IV was treated similarly to group III except that SCh was given on day 21.

Rats were weighed just before radiation and again before the SCh experiment, were pretreated with

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Received from the Departments of Anesthesiology, University of Illinois Abraham Lincoln School of Medicine and the Illinois Masonic Medical Center, Chicago. Accepted for publication October 6, 1981.

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atropine sulfate (0.05 mg/kg IM) before anesthesia, and were given just enough methoxyflurane to facilitate the intravenous titration of pentobarbital (20 to 50 mg/kg). After tracheotomy, respirations were controlled by a Harvard respiratory (5 to 7 ml, 50 breaths/min). The carotid artery was cannulated to measure blood gas tensions and blood pressure, and a laparotomy was performed to cannulate the inferior vena cava just above the bifurcation for sampling venous blood returning from the leg muscles or for measurements of plasma K^+ levels and for injection of drugs. Electrocardiograph (ECG) lead II also was monitored. Rats were given 0.2 ml of heparin (1000 Units/ml IV). After taking control arterial and venous blood samples (0.5 ml), SCh, 3 mg/kg, was rapidly administered intravenously, flushed in with saline, and 0.5-ml venous samples were withdrawn 1, 3, and 5 minutes after SCh. An arterial sample was also taken at 5 minutes. Potassium and sodium levels were determined with an IL photometer (model 343) and blood gas tensions with an IL model 430. Data were evaluated for statistical significance using Student's t-test for paired and nonpaired observation.

Results

The earliest symptoms following high levels of radiation (10,000 to 20,000 R) to the legs were hyperemia on day 2, edema of feet and thighs by days 3 and 4, followed by loss of hair and ulceration at 1 week, and death soon therafter. Lower levels of radiation (2500 to 5000 R) produced the same sequence of events but more slowly. Rats lost approximately 10% of their initial weight during the first week after irradiation; this increased to 15% to 20% loss by the 2nd and 3rd weeks. Total radiation of 5000 R given as two fractionated doses of 2500 R over 1 week proved to be lethal to 20% of the rats after the 2nd week, and by the 3rd week to 50% to 60% of the animals. As ^{60}Co radiation generates high levels of energy compared with x-rays, some scatter radiation effect probably accounted for these deaths.

All nonirradiated rats exhibited various degrees of fasciculation after the administration of the bolus SCh, 3 mg/kg, but fasciculation did not always occur among the irradiated rats. An interesting observation, particularly in rats in group IV, was that when fasciculations were absent, there was contracture of the muscles, a response reported to occur after administration of acetylcholine or SCh in denervated muscle (5).

After SCh administration there was usually a moderate decrease in blood pressure although some rats had an initial increase followed by a decrease. Changes in blood pressure did not appear to be related to the type and amount of radiation. There was a slight but significant increase in plasma K^+ levels (Table 1) in control rats following SCh administration but blood gas tensions in these animals remained unchanged during the 5 minutes after SCh (Table 2).

The response to SCh in rats in group II (Table 1) was similar to that seen in the control rats, with a slight but significant increase in plasma K^+ but unchanged blood gas tensions. One difference was that before SCh, rats in group II had a mean base line plasma level of K^+ that was 0.5 meq/L higher than that in the nonirradiated rats. As the significantly higher values after SCh did not exceed the initial difference of 0.5 meq/L, they obviously were not due to the SCh effect, but were probably caused by the radiation. Consequently, there was no evidence for increased sensitivity to SCh 1 week after high level radiation muscle injury.

To evaluate the possible development of increased sensitivity to SCh after a more prolonged time interval following radiation muscle injury, lower levels of radiation were administered in fractional doses. The hind legs of rats in group III were irradiated with 5000 R administered in two fractional doses of 2500 R over

TABLE 1
Effect of Succinylcholine (SCh) on Potassium Blood Levels (meq/L) in Rats Receiving Different Radiation Treatments*

Treatment group†	N	Time (min) after SCh (3 mg/kg)			
		0	+1	+3	+5
I. Control	10	3.1 ± 0.07	3.7 ± 0.09	3.9 ± 0.07	4.2 ± 0.09
II. 10,000 to 20,000 R, 4–7 days	12	3.6 ± 0.2	3.9 ± 0.16	4.3 ± 0.17	4.7 ± 0.17
III. 2,500 R ×2, 2 wk	9	3.1 ± 0.14	3.9 ± 0.12	4.3 ± 0.18	4.8 ± 0.21
IV. 2,500 R ×2, 3 wk	11	3.6 ± 0.16	7.0 ± 0.37	7.6 ± 0.41	7.7 ± 0.45

* Values are means ± SEM.
† See "Methods" for details.

TABLE 2

Blood Gas Tensions before and 5 Minutes after Administration of Succinylcholine, 3 mg/kg, following Different Radiation Treatments*

Treatment group†	N	pH		CO_2		P_{O_2}	
		0	+5	0	+5	0	+5
I. Control	10	7.38 ± 0.01	7.39 ± 0.01	42 ± 1	43 ± 1	68 ± 4	68 ± 2
II. 10,000 to 20,000 R, 4 to 7 days	12	7.37 ± 0.01	7.34 ± 0.02	41 ± 2	44 ± 3	80 ± 6	74 ± 5
III. 2500 R ×2, 2 wk	9	7.42 ± 0.01	7.45 ± 0.02	39 ± 2	40 ± 2	85 ± 2	86 ± 2
IV. 2500 R ×2, 3 wk	11	7.35 ± 0.02	7.28 ± 0.03	45 ± 2	47 ± 3	86 ± 5	88 ± 16

* Values are means ± SEM.
† See "Methods" for details.

a 1-week period. When SCh was given 2 weeks after the initial radiation (1 week after the final radiation treatment), there was a similar pattern, a clinically slight but statistically significant increase in K^+ levels, as in both control rats and group II rats. Thus after the combination of a reduced degree of radiation muscle injury and a postirradiation time interval 1 week longer than for group II, there was still no significant sensitization to SCh.

Rats in group IV had the same fractionated radiation schedule as those in group III but were given SCh 3 weeks after initial radiation. Five minutes after administration of SCh, plasma K^+ levels had increased from an average base line value of 3.6 to 7.7 meq/L, the SCh causing a greater than 100% increase in plasma K^+ levels after the additional week postirradiation. This increase was statistically highly significant.

There were no arrhythmias associated with changes in plasma K^+ levels, although in some cases the ECG showed increased T-wave amplitude. Blood gas data for group IV (Table 2) show a trend toward acidosis 5 minutes after administration of SCh; however, it is unlikely that the immediate and marked elevation of plasma K^+ seen 1 minute after SCh administration could be caused solely by this slight decrease in pH.

Discussion

SCh has been shown to cause depolarization of the postsynaptic membrane in a manner similar to that of acetylcholine and decamethonium (6, 7), the depolarization process being associated with a release of cellular K^+. This in turn increases plasma levels of K^+, as documented in clinical studies by Weintraub et al (8), and it may produce ECG changes even in healthy subjects (9).

The significance of SCh-induced hyperkalemia shifted from purely academic interest to clinical importance when Tolmie et al (1) reported that cardiac arrest in burn patients was caused by an exaggerated release of K^+ by SCh. The mechanism of the exaggerated SCh-induced hyperkalemia in these and other (3–4) clinical situations, especially thermal injury, is not definitely known. However, there is evidence that nerve degeneration (10) or muscle trauma and degeneration (11) cause the gradual spread of chemosensitive areas from normally discrete neuromuscular junctional sites to encompass the entire muscle membrane (5). Kendig and associates (12) examined this problem in rats with normal and denervated gastrocnemius muscles and concluded that the large net intracellular loss of K^+ after SCh administration appeared due to an increased area of SCh-sensitive membrane in the denervated muscle, with no impairment of active Na^+/K^+ transport.

Although skeletal muscle is relatively radioresistant compared with other tissues, there is extensive literature documenting varying degrees of radiation-induced damage to the cell membrane and intracellular structures (13, 14). The effect of ionizing radiation on skeletal muscle was reviewed by Zeman and Solomon (14), who concluded that exceptionally high doses of radiation produce acute necrosis, whereas exposures even in the therapeutic range may lead to a delayed necrosis that can be enhanced by such conditions as thyrotoxicosis, cachexia, and other debilitating conditions. These authors also give evidence that different muscles develop delayed radiation necrosis by different pathologic mechanisms. Thus, short muscles such as the laryngeal muscles are totally damaged, resulting in metabolic disorder and death, while muscles with long fibers are secondarily affected by associated vascular damage and subsequent denervation atrophy. Electron microscopic studies of rabbits 1 to 40 days after local exposure to 1300 R x-irradiation led to the conclusion that radiation-induced skeletal muscle changes result from a combination of direct

myofiber injury, microcirculatory compromise, and metabolic disturbances (15). When the hind legs of rats are irradiated with 3000 R x-irradiation, the resulting symptoms and changes in serum electrolytes and in metabolism resemble those observed in hereditary muscular dystrophy (16).

The effect of total body irradiation on serum electrolyte levels has been variable, depending on radiation dosage, postirradiation time, and species (17). There is an initial loss of K^+ from muscle and other tissues due to the direct effect of radiation, but plasma K^+ levels return to normal within several days (16, 18). An in vitro study of the effects of irradiation on K^+ ion transport in rat thymocytes postulates two mechanisms for the decrease in intracellular K^+ levels: low levels of radiation inhibit active transport, reducing the rate of K^+ uptake, whereas higher dose levels alter membrane permeability (19). Previous studies (16, 18) and our results indicate that these radiation-induced changes in K^+ are not, or are only slightly, reflected by changes in plasma K^+ levels (Table 1).

The hyperkalemia produced by SCh in this study was probably triggered by an acute myopathic process caused by the high radiation levels. Lewis (13) noted that this type of injury is similar to that caused by thermal or chemical trauma. Another similarity seen in our results was that a minimal period of postinjury time was essential for the development of increased muscle sensitivity to SCh. Although the radiation injury in our experiments was of an acute nature, it is important to reiterate that therapeutic levels of radiation may result in delayed necrosis many months later, expecially in the presence of debilitating diseases (14).

We believe that SCh administered to rats that have incurred muscle radiation injury may result in severe hyperkalemia. Although mindful of the pitfalls in extrapolating data from animal studies to humans, we feel that SCh should be avoided in patients who have sustained radiation injury, especially following radiation to the large skeletal muscles.

REFERENCES

1. Tolmie JD, Joyce, TH, Mitchell GD. Succinylcholine danger in the burned patient. Anesthesiology 1967;28:467–70.
2. Mazze RI, Escue HM, Houston JB. Hyperkalemia and cardiovascular collapse following administration of succinylcholine to the traumatized patient. Anesthesiology 1969;31:540–7.
3. Cooperman LH, Strobel GE Jr, Kennel EM. Massive hyperkalemia after administration of succinylcholine. Anesthesiology 1970;32:161–4.
4. Stone WA, Beach TP, Hamelberg W. Succinylcholine-danger in the spinal cord-injured patient. Anesthesiology 1970;32:168–9.
5. Gronert GA, Theye RA. Pathophysiology of hyperkalemia induced by succinylcholine. Anesthesiology 1975;43:89–99.
6. Thesleff S. Effects of acetylcholine, decamethonium and succinylcholine in neuromuscular transmission in the rat. Acta Physiol Scand 1955;34:386–92.
7. Paton WDM. Model of action of neuromuscular blocking agents. Br J Anaesth 1956;28:470.
8. Weintraub HD, Heisterkamp DV, Cooperman LH. Changes in plasma potassium concentration after depolarizing blockers in anaesthetized man. Br J Anaesth 1969;41:1048–52.
9. Evers W, Racz GC, Dobkin AB. A study of plasma potassium and electrocardiographic changes after a single dose of succinylcholine. Can Anaesth Soc J 1969;16:273.
10. Miledi R. Acetylcholine sensitivity of frog muscle fibres after complete or partial denervation. J Physiol (Lond) 1960;151:1–23.
11. Katz B, Miledi R. Development of acetylcholine sensitivity in nerve-free segments of skeletal muscle. J Physiol (Lond) 1964;170:389–96.
12. Kendig JJ, Bunker JP, Endow S. Succinylcholine-induced hyperkalemia: effects of succinylcholine on resting potentials and electrolyte distributions in normal and denervated muscle. Anesthesiology 1972;36:132–7.
13. Lewis RB. Changes in striated muscle following intensive doses of x-rays. Lab Invest 1954;3:48–55.
14. Zeman W, Solomon M. Effects of radiation on striated muscle, In: Berdjis C, ed. Pathology of irradiation. Baltimore: Williams & Wilkins, 1971:171–85.
15. Khan MY. Radiation-induced changes in skeletal muscle. An electron microscopic study. J Neuropathol Exp Neurol 1974;33: 42–57.
16. Dowben RM, Zuckerman L. Alterations in skeletal muscle after x-irradiation and their similarity to changes in muscular dystrophy. Nature 1963;197:400–1.
17. Fulton GP, Sudak FN. Effect of total body x-irradiation on serum electrolyte levels and electrocardiograms of the golden hamster. Am J Physiol 1954;179:135–8.
18. Caster WO, Armstrong WD. Electrolyte metabolism after total-body x-irradiation. Radiat Res 1956;5:189–204.
19. Chapman IV, Sturrock MG. Effects of x-irradiation in vitro on the transport of potassium ions in thymocytes. Int J Radiat Biol 1972;22:1–9.

ANESTH ANALG
1982;61:87-92

Plasma Levels of Ketamine and Two of Its Metabolites in Surgical Patients Using a Gas Chromatographic Mass Fragmentographic Assay

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DOMINO, E. F., ZSIGMOND, E. K., DOMINO, L. E., DOMINO, K. E., KOTHARY, S. P., AND DOMINO, S. E.: Plasma levels of ketamine and two of its metabolites in surgical patients using a gas chromatographic mass fragmentographic assay. Anesth Analg 1982;61:87-92.

Ketamine and two of its metabolites were determined up to 24 hours by a sensitive and specific gas chromatographic mass fragmentographic (GCMF) assay in the plasma of seven premedicated surgical patients. Each patient received ketamine in a dose between 2.0 and 2.2 mg/kg given intravenously over a 30-second period. Plasma levels of ketamine varied from 9,000 to 25,800 ng/ml 1 minute after injection to approximately 1,000 ng/ml when the patients began to recover consciousness. Within the next 24 hours, the patients had a complex logarithmic decline in plasma levels of ketamine. Some patients showed approximately 5 to 15 ng/ml levels of ketamine 24 hours after injection. The data suggest rather complex pharmacokinetics with multiple compartments. Ketamine metabolites I and II were also found in the plasma over comparable periods of time. Ketamine metabolite I levels ranged from a high of 245 to 668 ng/ml within 30 minutes after ketamine administration to as low as 15 ng/ml 24 hours later. Ketamine metabolite II levels were lower with a peak of 515 ng/ml in approximately 60 minutes to 13 to 27 ng/ml 24 hours later. Recovery from anesthesia was related to the first two phases of rapid redistribution of ketamine. The plasma levels of the two ketamine metabolites were first detectable approximately 5 minutes after ketamine injection. Their relatively low levels throughout ketamine anesthesia and postanesthesia do not correlate with recovery from anesthesia. CSTRIP and NONLIN analysis indicated that a three-exponential equation best approximated the data obtained. It is concluded that a three-compartment open model best approximates ketamine pharmacokinetics in these patients.

Key Words: ANESTHETICS, Intravenous: ketamine; PHARMACOKINETICS: ketamine.

TO DATE a large number of investigators (1-8) have measured the plasma levels of ketamine in various patients and reported on its kinetics. Much of the data reported fit a two-compartment open model with an initial plasma half-life in minutes and a second plasma half-life of 2 to 3 hours. The term "a two-compartment open model" means that the body is conceptualized as being composed of two major tissue types. The first includes plasma and related blood-rich tissues and the second the rest of the body. The drug is distributed between compartments after infusion into compartment 1 by linear first-order rate parameters. Linearity is defined as the direct proportionality of transfer rates to concentration differences. In addition, elimination is assumed to occur from the first compartment only. The advantage of using a suitable model is that it permits the application of mathematical techniques to obtain a set of equations that describe the proposed system.

We have developed a sensitive gas chromatographic-mass fragmentographic (GCMF) assay for ketamine and two of its many metabolites (9). The significance of ketamine metabolites at present is unknown except that they usually are less active. This

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Supported in part by the Psychopharmacology Research Fund.
Received from the Departments of Pharmacology and Anesthesiology, University of Michigan, Ann Arbor, Michigan; University of Illinois, Chicago, Illinois; and Washington University, St. Louis, Missouri. Accepted for publication October 13, 1981. Presented in part at the 52nd Congress of the International Anesthesia Research Society, March 19-23, 1978, San Francisco, California.
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has given us the opportunity to study the plasma levels of ketamine and its metabolites over a 24-hour period. This paper describes seven patients whose results indicate that ketamine has at least three plasma half-lives. These results are consistent with the findings of the first human study in which 2.2 mg/kg of ketamine given intravenously to volunteers showed suppression of their alpha rhythm of the electroencephalogram for at least 1 hour after recovery from anesthesia (10). This and many subsequent clinical observations related to emergence from ketamine anesthesia suggest that ketamine and/or its metabolites may persist in the human body for hours. This more sensitive assay has permitted us to describe a more complete model of ketamine kinetics in man.

Methods

Patients

A total of seven patients volunteered for this study in connection with undergoing a therapeutically indicated surgical procedure. The protocol was approved by the Committee to Review Protocols for Clinical Research and Investigation Involving Human Beings at the University of Michigan Medical Center. Patients were selected on the basis of suitability, informed consent, and permission of the surgeon. Both men and women were selected. No minors or known pregnant women were selected. Patients with a history of psychiatric complications, brain damage, epilepsy, or drug abuse were rejected. All patients were between 18 to 55 years of age in A.S.A. physical status I to III. Prior to being seen the day before, patients were on whatever medication their physician deemed necessary.

The physical characteristics of the seven patients studied are shown in Table 1. There were three male and four female patients with a mean age of 45.3 ± 9.3 (SD) years and a mean weight of 64.3 ± 10.1 kg. The surgical procedures, premedication (given within 2 hours of anesthesia), and the anesthetic agents used for the maintenance of anesthesia are presented in Table 2. The patients were brought to the anesthesia induction room at approximately 8:00 a.m. usually as the second or third case scheduled. An intravenous infusion consisting of 0.9% NaCl was started with a maximum of 1000 ml throughout the 24-hour period. Some patients were also monitored with electrocardiogram (ECG) and electroencephalogram (EEG) leads in addition to other vital signs. Ketamine-HCl (Ketalar) was given in a dose of 2.0 to 2.2 mg/kg intravenously over a 30-second period. Blood samples were withdrawn from a separate venous line at various times (−5, 1, 2, 5, 10, 15, 20, and 30 minutes, and 1, 2, 3, 4, 5, 6, 7, 8, 12, and 24 hours) after ketamine administration. Not all time points were taken because of various practical clinical reasons as well as the fact that this was a pilot study. After the first 10 minutes, the patient was moved to the operating room and prepared for surgery. Approximately 20 to 30 minutes later a variety of balanced anesthesia techniques was used for the surgical procedure. On some occasions, when the venous samples were difficult to obtain during surgery, blood samples were obtained from an arterial line used to monitor blood gas tensions. No other medication besides oxygen was given for the first 20 minutes. Subsequently, the patients received the anesthetic agents for their surgical procedure as listed in Table 2. After surgery, general anesthesia was terminated and the patients were taken to the postoperative recovery room and later to their rooms where venous samples continued to be withdrawn.

TABLE 1
Physical Characteristics of Patients

Patient no.	Age*	Sex	Weight†	A.S.A. physical class	Diagnosis
	yr		*kg*		
1	49	F	54.5	II	Carcinoma of vulva
2	57	F	55.9	II	Carcinoma of endometrium
3	42	F	54.5	III	Crohn's disease
4	31	M	61.4	III	Nasal polyps
5	36	F	77.3	II	Elective sterilization
6	51	M	71.8	II	Lower urinary tract obstruction
7	51	M	75.0	II	Terato carcinoma of testis

* Mean age 45.3 ± 9.29 (SD) years; ±3.52 (SE) years.
† Mean weight 64.3 ± 10.09 (SD) kg; ±3.82 (SE) kg.

Extraction and Derivatization

The extraction and chemical derivatization of ketamine was based on the methods of Chang et al (1, 3, 11) as modified for GCMF electron impact by us (9). CL-394, the o-Br analog of ketamine, was used as the internal standard. Ketamine, CL-394, and ketamine metabolites were provided by Dr. A. J. Glazko, Warner Lambert/Parke Davis Co, Ann Arbor, MI. Heptafluorobutyric anhydride was obtained in 1-ml ampules or a 25-gm bottle from Pierce Chemical Co, Rockford, IL. "Nanograde" solvents were obtained from Mallinckrodt Chemical Works, St. Louis, MO.

TABLE 2

Surgical Procedures and Anesthetic Agents Used in Patients Studied

Patient no.	Surgical procedure	Premedication	Ketamine dose (IV)	Anesthetic agents for maintenance of anesthesia
			mg	
1	Radical vulvectomy Pelvic lymphnode dissection	Diazepam, 10 mg, orally	109	Fentanyl; N_2O; O_2 Pancuronium
2	Dilation and curettage Lapscope	None	111	Fentanyl; N_2O; O_2 Diazepam; succinylcholine
3	Ileostomy	Diazepam, 10 mg, orally Morphine, 8 mg IM	109	Fentanyl; N_2O; O_2 Succinylcholine; pancuronium
4	Nasal polypectomy	None	139	Halothane; N_2O; O_2 Tubocurarine; succinylcholine
5	Lapscope Tubal cauterization Dilation and curettage	None	140	Fentanyl; N_2O; O_2 Succinylcholine
6	Transurethral resection to prostate	Hydroxyzine, 100 mg IM	144	Fentanyl; N_2O; O_2 Pancuronium
7	Retroperitoneal node dissection Hemiscrotectomy	Morphine, 10 mg IM Hydroxyzine, 100 mg IM	160	Morphine; N_2O; O_2 Pancuronium

TABLE 3

Plasma Levels of Ketamine (K) and Two of Its Metabolites (KI and KII) in Seven Surgical Patient Volunteers

Time	1			2	3			4			5	6			7		
	K	KI	KII	K	K	KI	KII	K	KI	KII	K	K	KI	KII	K	KI	KII
									ng/ml								
−5 min	0	0	0		0	0	0	0	0	0	0	0	0	0	0	0	0
1 min	5545	0	0		8999	0	0					25,815	0	0	7660	0	0
2 min	1581	30	0	2290				15,100	0	0	5300	9450	0	0	3540	0	0
5 min	1086	86	48	1810	759	182	147	2900	138	27	2250	1570	0	0	1710	238	0
10 min	773	254	45	1300	496	272	250				1325	890	106	18	1120	410	19
15 min				880				1600	184	99	805						
20 min	231	2162	353		384	91	258				697	491	227	130	510	537	46
30 min	176	1998	325		276	91	350	760	245	171		433	668	426	340	537	65
1 hr	168	244	80		160	46	515	360	235	162		252	197	259			
2 hr	165	451	377		76	38	350	230	174	113		220	136	222	140	296	66
3 hr												172	127	233	110	219	49
4 hr	28	39	220	500				115	130	38		109	106	204	49	140	78
5 hr	38	148													120	208	73
6 hr	46	138													40	121	72
7 hr	35	97													49	147	35
8 hr	57	80						83	255	162					24	102	39
12 hr		33													28	31	43
24 hr		6						15	60	27		4	15	19	5	24	13

The column packings, 3% OV-17 on 100/120 Gas Chrom Q, were obtained from Applied Science Laboratories, Inc, State College, PA.

Analysis of Ketamine and Two of Its Metabolites

Quantitative analyses were made on a Finnigan 3200 GCMS system operated in the electron impact mode. A 5 ft x 2 mm glass U-tube column packed with 3% OV-17 on 100/120 mesh on Gas-Chrom Q was conditioned by heating overnight at 250 C. The GC conditions were: column temperature 180 C isothermal, injector temperature 210 C. The carrier gas flow (He) was 20 ml/min. The glass jet separator temperature was 210 C. The electron energy was 70 eV.

Pharmacokinetics

A three-exponential fit of the data was obtained by computer analysis using CSTRIP (12) and confirmed using NONLIN (13). Various standard pharmacoki-

netic parameters were calculated from the coefficients and exponents of the polyexponential equation as described by Wagner (14). The Michigan Terminal Ssytem (MTS) was used with the Amdahl 470 V/8 computer. Plotting subroutines of MTS were used to draw the calculated and determined plasma ketamine levels.

Results

The extraction and derivatization procedure for ketamine and its two metabolites (KMI and KMII) from human plasma provided excellent gas chromatographic separation. Ketamine KMI and KMII are all extracted and derivatized with the same procedure. KMI is norketamine, but KMII is an unknown compound(s) which during the extraction procedure appear(s) to be converted to dehydronorketamine as an artifact (15).

The plasma levels of ketamine, KI, and KII obtained for the seven different surgical patients are listed in Table 3. The three-compartment open model pharmacokinetic parameters for ketamine only for five of the seven patients are given in Tables 4 and 5. Note the marked individual differences between different surgical patients. In Fig 1 is shown the computer-generated plot of the triexponential equation from NONLIN of some of the data points for patient 7.

Fig 2 represents the computer-generated plot of the mean ketamine amounts in each of the three compartments for 60 minutes. With recovery of consciousness within 30 minutes it appears that compartment 2 may be relevant to the duration of anesthesia.

Discussion

Ketamine and its metabolites persist in trace amounts in the human plasma of some surgical patients for at least 24 hours following a single intrave-

TABLE 4

Pharmacokinetic Parameters Obtained through Direct Curve Fitting or a Three-Exponential Equation of Ketamine in Surgical Patients*

Patient no.	Exponential term											
	1				2				3			
	P_{inf}	P_{bol}	π	$\pi_{t1/2}$ hr	A_{inf}	A_{bol}	α	$\alpha_{t1/2}$	B_{inf}	B_{bol}	β	$\beta_{t1/2}$
	ng/ml		*hr*$^{-1}$	*hr*	*ng/ml*		*hr*$^{-1}$	*hr*	*ng/ml*		*hr*$^{-1}$	*hr*
1	714,000	147,000	314	0.00220	1,850	1,790	8.06	0.086	173	173	0.270	2.56
3	44,100	33,000	66.6	0.01040	467	461	2.88	0.241	232	231	0.566	1.22
4	136,000	98,600	72.7	0.00953	3,240	3,180	4.36	0.159	334	334	0.197	3.51
6	73,700	55,000	67.0	0.01030	1,550	1,510	5.93	0.117	336	336	0.240	2.88
7	20,500	14,300	81.1	0.00855	2,400	2,340	5.71	0.121	197	197	0.227	3.05
Mean	198,000	69,600	120.0	0.00820	1,470	1,960	5.39	0.145	254	254	0.300	2.64
±SE	292,000	53,500	108.0	0.00343	1,200	1,010	1.93	0.060	77	77	0.151	0.60

* Values given here are for coefficients and exponents of the following polyexponential equation: C_p is the estimated concentration of ketamine in plasma at time t in hours. $C_p = Pe^{-\pi t} + Ae^{-\alpha t} + Be^{-\beta t}$. P_{inf}, P infusion; P_{bol}, P bolus equivalent; etc.

TABLE 5

Pharmacokinetic Rate and Distribution Parameters for Three-Compartment Open Model of Ketamine in Surgical Patients*

Patient no.	First order rate parameters					Distribution parameters					
	K_{12}	K_{21}	K_{13}	K_{31}	K_e	Vd_1	Vd_2	Vd_3	Vd_{ss}	Vd_{area}	Cl_{plasma}
			hr^{-1}				*L*			*L*	*L/hr*
1	99.1	11.90	99.0	0.515	112.0	0.732	6.12	141.0	148.0	303	82.1
3	18.0	3.89	15.6	0.882	31.6	3.24	15.00	57.3	75.6	181	102.0
4	22.8	6.57	20.5	0.352	27.0	1.36	4.73	79.1	85.2	186	36.8
6	13.9	7.64	28.1	0.543	23.0	2.53	4.60	131.0	138.0	242	58.3
7	43.2	16.80	14.8	0.539	11.6	9.49	24.40	261.0	295.0	485	110.0
Mean	39.4	9.36	35.6	0.566	41.0	3.47	11.00	134.0	148.0	279	77.8
±SD	35.2	5.06	35.8	0.193	40.4	3.20	8.70	79.0	88.0	125	30.4

* Abbreviations used are: K_{12}, rate of transfer from compartment 1 to 2; K_{21}, rate of transfer from compartment 2 to 1; K_{13}, rate of transfer from compartment 1 to 3; K_{31}, rate of transfer from compartment 3 to 1; K_e, elimination constant from compartment 1; Vd_1, Vd_2, Vd_3, volumes of distribution of compartments 1, 2, and 3; Vd_{ss}, volume of distribution of K at steady state; Vd_{area}, apparent volume of distribution of K; Cl_{plasma}, plasma K clearance.

nous dose. Of obvious clinical interest is the fact that the recovery from ketamine anesthesia seems to correlate with the rapid redistribution of the drug as indicated by its steep decline in plasma rather than recovery by biotransformation. Plasma levels of KMI predominated over KMII in four of the seven patients studied. The role of the metabolites of ketamine in the clinical pharmacology of ketamine as well as the structure of KMII remain unknown and require future investigation.

Analysis of blood levels of ketamine, KI, and KII in each patient reveals marked individual variation as to the first (π), second (α), and third (β) phases or slopes of the ketamine-plasma decay curve and the rate of ketamine conversion into KI and KII. Obviously, many factors contribute to the individual differences including variations in the premedication, anesthesia maintenance, surgical, pathologica, etc.

In Table 6 are summarized some of the reported data on the pharmacokinetics of ketamine in man. In general, the findings of all investigators are consistent with a two- or three-compartment model depending upon the sensitivity of the assay and duration of observation. In most of these studies other medications besides ketamine were used. It is known that halothane anesthesia alters the biodisposition of ketamine in rats (16). Diazepam also has been shown to alter the biotransformation of ketamine in animals

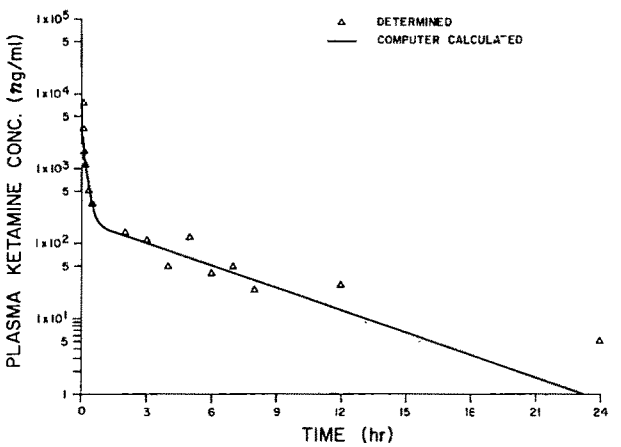


FIG 1. Plasma concentration of ketamine and nonlinear least squares fit of a three-exponential equation of data in surgical patient. Patient 7 received 160 mg of ketamine. Plasma concentrations (Δ) were measured for 24 hours. NONLIN provided a three-exponential equation whose solution is illustrated by the solid line. The equation is: C_{plasma} (ng/ml) = $14{,}300e^{-81.1\,t} + 2340e^{-5.71t} + 197e^{-.227\,t}$ with t in hours.

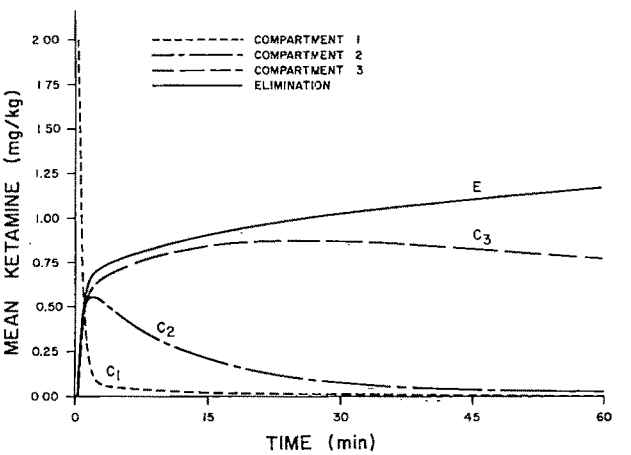


FIG 2. Estimated amounts of ketamine in each compartment of a three-compartment open model. Data represent means for all patients studied. Note rapid reduction in ketamine in compartment 1. Compartment 2 levels peak within 2 minutes and decline over 30 or more minutes. In contrast, compartment 3 accumulates ketamine over the 1-hour period with rapid elimination (E) of approximately half the dose in first 30 minutes.

TABLE 6

Comparison of Some Reported Pharmacokinetic Parameters of Ketamine in Man*

Parameter	Investigators							
	Chang and Glazko (1)	Wieber et al (4)	Idvall et al (5)	Clements et al (6)		Hug et al (7)	Domino (8)	Present study
Assay	GCEC	GCFID	GCEC	GCEC	GCEC	GCND	GCMF	GCMF
Dose (mg/kg)	2.2	2.5	2.0	0.125	0.25	2.0	2.2	2.0–2.2
Last time point assayed (hr)	0.58	12	2	7	7	5	0.5	24
No. of compartments	1	2	1	2	2	3	2	3
Other medications	Not stated	Not stated	Yes	No	No	Yes	No	Yes
t½ π (min)						1.6		0.49
t½ α (min)	17	11		18	16	12	5.5	8.7
Apparent terminal t½ β (min)		151	79	182	178	118	122	158
Vd_{ss} (L)		204		157	232			148
Clearance (L/min)		1.2		1.2	1.4	0.81		1.3

* Abbreviations used are: π, first slope of reduction of ketamine in blood; α, second slope of reduction of ketamine in blood; β, third slope of reduction of ketamine in blood; GCEC, gas chromatography electron capture; GCFID, gas chromatography flame ionization detection; GCND, gas chromatography nitrogen detection; GCMF, gas chromatography mass fragmentography.

(17). As two of the seven patients received diazepam, their ketamine biotransformation might be affected. However, in this pilot study the pharmacokinetics of ketamine were not grossly different from those of patients who did not receive oral diazepam. Nevertheless, future studies of the pharmacokinetics of ketamine must control for these obvious drug interactions which must occur when using surgical patients.

ACKNOWLEDGMENTS

The authors would like to acknowledge Drs. C. M. Metzler and J. G. Wagner for the generous use of their computer programs.

REFERENCES

1. Chang T, Glazko A. A gas chromatographic assay for ketamine in human plasma. Anesthesiology 1972;36:401–4.
2. Hodshon BJ, Ferrer-Allado T, Brechner VL, Cho AA. A gas chromotographic assay procedure for ketamine in plasma. Anesthesiology 1972;36:506–8.
3. Chang T, Savory A, Albin M, Goulet R, Glazko A. Metabolic disposition of tritium-labelled ketamine (Ketalar, CI-581) in normal human subjects. Clin Res 1970;18:596.
4. Wieber J, Gugler R, Hengstmann JH, Dengler JH. Pharmacokinetics of ketamine in man. Anaesthetist 1975;24:260–3.
5. Idvall J, Ahlgren I, Aronsen KF, Stenberg P. Ketamine infusions: pharmacokinetics and clinical effects. Br J Anaesth 1979;51:1167–73.
6. Clements JA, Nimmo WS. Pharmacokinetics and analgesic effect of ketamine in man. Br J Anaesth 1981;53:27–30.
7. Hug CC Jr, Stiller RS, Chipponi C, Perell JM. Ketamine (K) pharmacokinetics in cardiac surgery. Pharmacologist 1981;23: 203.
8. Domino EF. Ketamine: isomers and metabolites. In: Zindler M, Rugheimer E, eds. Anaesthesiology, Proceedings of the 7th World Congress of Anesthesiologists. International Congress Series. Amsterdam, Excerpta Medica, 1981:696–9.
9. Lau SS, Domino EF. Gas chromatography-mass spectrometry assay for ketamine and its metabolites in plasma. Biomed Mass Spectrom 1977;4:317–21.
10. Domino EF, Chodoff P, Corssen G. Pharmacologic effects of CI-581, a new dissociative anesthetic in man. Clin Pharmacol Ther 1965;6:279–91.
11. Dill WA, Chucut L, Chang T, Glazko A. Determination of ketamine in blood plasma. Anesthesiology 1971;34:73–6.
12. Sedman AJ, Wagner JG. CSTRIP, A FORTRAN IV computer program for obtaining initial polyexponential parameter estimates. J Pharm Sci 1976;65:1006–10.
13. Metzler CM, Elfring GK, McEwen AJ. A package of computer programs for pharmacokinetic modeling. Biometrics 1974;30: 562–3.
14. Wagner JG. Linear pharmacokinetic equations allowing direct calculation of many needed pharmacokinetic parameters from the coefficients and exponents of polyexponential equations which have been fitted to the data. J Pharmacokinet Biopharm 1976;4:443–67.
15. Stenberg P, Indvall J. Does ketamine metabolite II exist *in vivo*? Br J Anaesth 1981;53:778.
16. White PE, Marietta MP, Pudwill CR, Way WL, Trevor AJ. Effects of halothane anesthesia on the biodisposition of ketamine in rats. J Pharmacol Exp Ther 1976;196:545–55.
17. Borondy PE, Glazko AJ. Inhibition of ketamine metabolism by diazepam. Fed Proc 1977;36:3515.

ANESTH ANALG
1982;61:93-8

Epidural Morphine for Postoperative Pain Relief: A Comparative Study with Intramuscular Narcotic and Intercostal Nerve Block

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RAWAL, N., SJÖSTRAND, U. H., DAHLSTRÖM, B., NYDAHL, P.-A., AND ÖSTELIUS, J.: Epidural morphine for postoperative pain relief: a comparative study with intramuscular narcotic and intercostal nerve block. Anesth Analg 1982;61:93-8.

The relatively new technique of epidural morphine analgesia was compared with two well established methods of pain relief in 90 patients undergoing gallbladder surgery and divided randomly into three groups of 30 patients each. The first group received intramuscular narcotic analgesic ketobemidone, the second group was given 0.5% bupivacaine-epinephrine intercostal nerve block, and the third group received a single dose of 4 mg of epidural morphine for postoperative pain relief. The mean duration of analgesia after ketobemidone was 5.5 hours, and after intercostal block 11 hours. Of the patients given epidural morphine, 40% did not require further analgesia after the initial injection; the remaining patients in this group were pain free for a mean duration of 19 hours. The mean reduction in postoperative peak expiratory flow was most marked following ketobemidone and least after epidural morphine. Postoperative changes in Pa_{O_2} and Pa_{CO_2} reflected the changes in peak expiratory flow. Plasma levels of morphine after epidural injection were so low that a regional spinal analgesic action of epidural morphine appeared more likely than a systemic effect. Delayed respiratory depression was not encountered after epidural morphine. It is concluded that a single dose of 4 mg of epidural morphine provides excellent regional analgesia of long duration without drowsiness or circulatory or respiratory depression, thus facilitating early ambulation. The technique is superior to more common methods of pain relief after gallbladder surgery, e.g., intercostal nerve block and intramuscular narcotics.

Key Words: ANALGESICS: narcotic, morphine; ANESTHETIC TECHNIQUES: epidural; PAIN: postoperative.

POSTOPERATIVE pain relief is important for the reduction of morbidity after surgery, especially after upper abdominal surgery which is generally recognized as being associated with an increased incidence of pulmonary complications. Patients who have had upper abdominal surgery have difficulty in coughing, moving about, and taking deep breaths for fear of aggravating their pain (1-3).

Epidural narcotics have been used increasingly in recent years and many studies have shown that this method of pain relief provides prolonged segmental analgesia without either the systemic side effects of narcotics or the sensory or motor block seen with regional anesthetic techniques for the relief of pain. As there is a lack of comparative studies in this field, the aim of this study was to compare the analgesic effect of epidural morphine with that of intercostal nerve block and an intramuscular narcotic in patients undergoing gallbladder surgery, the latter two methods being the most common forms of postoperative analgesia for upper abdominal surgery. The narcotic agent used was ketobemidone (Ketogin) which is equipotent with morphine (4).

Methods and Materials

Ninety patients undergoing gallbladder surgery with a subcostal incision were studied. They were

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Received from the Department of Anesthesiology and Intensive Care, Regional Hospital, S-701 85 Örebro, Sweden, and ACO Läkemedel AB, S-171 03 Solna, Sweden. Accepted for publication September 25, 1981.

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divided randomly into three groups of 30 patients each depending on whether they were born within the first, second, or third 10 days of the month, i.e., group I was comprised of patients born during the first 10 days of the month and received ketobemidone analgesia after surgery; group II was comprised of patients born within the 11th to the 20th day of the month and were given intercostal nerve block; the patients born within the 21st to 30th of the month made up group III and were given epidural morphine for postoperative analgesia. Informed consent was obtained. All patients were otherwise healthy. There were 18 men and 72 women; the sexes were equally represented in the three groups. The ages varied from 29 to 72 years (mean 54 ± 14.4 SD). The mean ages in groups I, II, and III were 53, 55, and 54 years, respectively. Patients were premedicated with intramuscular meperidine, 50 to 75 mg, and promethazine, 25 mg. Anesthesia was induced by thiopental and, after endotracheal intubation with pancuronium, was maintained by nitrous oxide/oxygen, fentanyl, and droperidol.

Patients in group I were extubated after reversal of the neuromuscular block. After completion of surgery and before extubation, patients in group II were placed in the lateral position and given a right-sided intercostal nerve block 6 to 8 cm paravertebrally at the levels of T-6 to T-11. Bupivacaine (0.5%) with 1: 200,000 epinephrine was used and 3 ml was injected on each intercostal nerve for a total of 18 ml. Patients in group III were also placed in the lateral position before extubation and a Tuohy needle was inserted into the epidural space at the level of T11-12 or T-12 to L-1. With the bevel of the needle pointed cephalad 4 mg of preservative-free morphine in 10 ml of isotonic saline was injected and the needle was then withdrawn.

Blocks were not repeated in either group II or III. Ketobemidone, 5 to 7.5 mg, was prescribed for all patients for postoperative analgesia and was available on demand. Pulse rate, blood pressure, and respiratory rate were recorded every 15 minutes for 5 to 6 hours. In 10 of the 30 patients from each group, peak expiratory flow (PEF) was recorded and arterial blood samples were analyzed before and after surgery. PEF was recorded preoperatively before premedication with the patient sitting and the maximum value of three attempts was recorded. Arterial blood samples were taken at the same time and analyzed by an automatic blood gas analyzer (ABL 2, Radiometer A/S, Denmark). After surgery, when the patient was fully awake, PEF recordings and arterial blood gas analyses were carried out as above before any intramuscular analgesic was administered. In five patients, venous blood samples were taken from the arm before and 10, 30, 60, 180, and 360 minutes after epidural morphine injection. The morphine concentration in the plasma was determined by gas chromatography with electron capture detection (5). These patients were also presented in a previous study (6).

The duration of analgesia as well as the need for additional analgesia were noted. In groups II and III, the duration of analgesia was defined as the time between extubation until the patient required additional analgesia. In group I, duration of analgesia was defined as the time between the first and second intramuscular injections. The analgesic effect was assessed by the patient and ward nurse and was graded as excellent, fair, or poor. Analgesia was considered excellent when the patient was completely free of pain after the block or injection, fair when the patient was relatively (but not completely) pain free, and poor when additional analgesics had to be given because of inadequate or absent analgesic effect. Side effects and complications were noted.

Results

There was a considerable difference in the duration of analgesia between the different methods. The epidural morphine group (III) had by far the longest duration; fully 40% of the patients were completely pain free after the single injection with no further analgesia required. In the remaining 60% the duration of epidural morphine analgesia ranged widely from 6 to 35 hours with a mean of 19.3 ± 10.6 (SD). With intercostal block, group II, the duration of analgesia varied from 5 to 21 hours with a mean duration of 11.1 ± 4.5 (SD). After ketobemidone, group I, the duration varied from 2.5 to 13 hours with a mean of 5.5 ± 6.5 (SD) hours. All patients in groups I and II required additional analgesia (Table 1). The need for additional analgesia in the first 48 hours after surgery was more than 3 times greater after ketobemidone and twice as great after intercostal block as the need for additional analgesia after epidural morphine. After 48 hours, the requirement of additional analgesia was nearly the same in all the groups (Table 1, Fig 1). The number of patients who considered analgesia to be excellent was 88% in group III (epidural morphine), 71% in group II (intercostal block), and 40% in group I (intramuscular ketobemidone). Assessment of analgesia by ward nurses was roughly the same. Most of the remaining patients considered the analgesia as acceptable (Table 2).

The mean decrease in postoperative PEF as compared with the preoperative levels was most marked in group I with a reduction of 40% as compared with 25% reduction in group II and 10% in group III. Similarly, postoperative decreases in Pa_{O_2} and increases in Pa_{CO_2} were most marked in group I and least in group III (Fig 2, Table 3).

Morphine was rapidly absorbed from the epidural space, giving peak levels of 14 to 37 ng/ml in plasma within 10 to 30 minutes. Plasma levels then declined in a phasic manner with a mean terminal half-life of 164 minutes. Six hours after administration of epidural morphine, the average plasma concentration of morphine was 2 ng/ml with a range of 1.0 to 2.7 ng/ml (Fig 3). Plasma clearance and volume of distribution averaged 22 ml/min/kg and 6.35 L/kg, respectively, which are in good agreement with corresponding values reported earlier (6, Dahlström B, Paalzow A, Tamsen A, Hartvig P. Multiple and single dose kinetics of morphine in man. Proceedings of the Symposium on Narcotic Analgesia, November 12–14, 1980, Stockholm, Sweden, p 15).

TABLE 1

Duration of Analgesia and Requirement of Additional Analgesia

	Duration of analgesia*	Av requirement of additional analgesia in postoperative period	Total ketobemidone needed in first 48 hr after surgery
	hr	*mg/3hr*	*mg*
Ketobemidone (group I)	5.5 ± 6.5	1.43	23
Intercostal block (group II)	11.1 ± 4.5	0.91	14
Epidural morphine (group III)	19.3 ± 10.6	0.46	7

* Values are means ± SD.

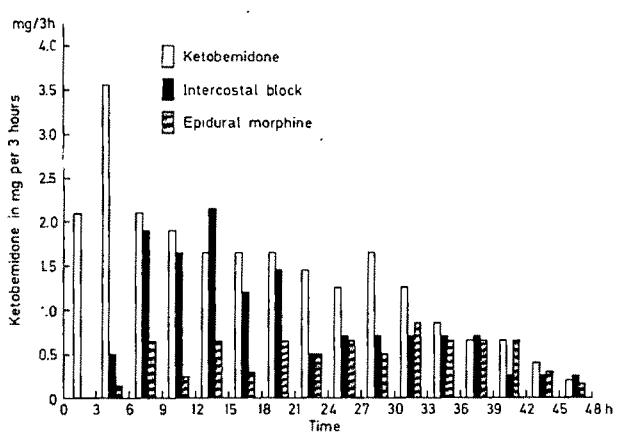


FIG 1. Requirement of additional analgesia in first 48 hours after surgery.

TABLE 2

Patient and Ward Nurse Assessment of Analgesia

	Ketobemidone (I)		Intercostal block (II)		Epidural morphine (III)	
	Patient	Ward nurse	Patient	Ward nurse	Patient	Ward nurse
	%					
Excellent	40	50	71	77	88	88
Fair	57	42	16	13	6	6
Poor	3	7	13	10	6	6

No significant hypotension was noted in any of the groups. There was no sensory or motor block after epidural morphine. The incidence of postoperative vomiting in group I (28%) and group II (23%) was approximately 3 to 5 times greater than in group III (7%). The incidence of postoperative urinary retention, which was transient in all cases, was the same in all three groups, approximately 22%. It should be noted that all patients in group II and 60% of the patients in group III required additional intramuscular narcotic which may have influenced the incidence of vomiting and urinary retention. None of the patients in group III complained of itching. Three patients (10%) in group II had radiologically verified atelectasis and signs of pneumonia in the postoperative period. One patient in group I developed pneumothorax which was treated successfully. One patient in group III exhibited signs of transient meningeal irritation.

Discussion

Gallbladder surgery is associated with severe postoperative pain (7, 8). It is well known that pain after upper abdominal surgery can lead to decreases in arterial oxygenation and dynamic spirometric measurements, as well as restricted ventilation and uneven ventilation perfusion distribution, i.e., increased pulmonary shunting and hypoxemia (1, 2, 9). In spite of general agreement that pain relief after upper abdominal surgery is important for the reduction of postoperative morbidity (1–3), the most widely used method remains intramuscular injection of narcotics with their well known disadvantages of drowsiness, nausea, vomiting, hypotension, respiratory depression, and inadequate analgesia (1, 2, 10–12). This is supported by our study: postoperative decreases in PEF and Pa_{O_2} were most pronounced following ketobemidone; only 40% of patients considered the analgesia excellent; and 10% of patients developed pul-

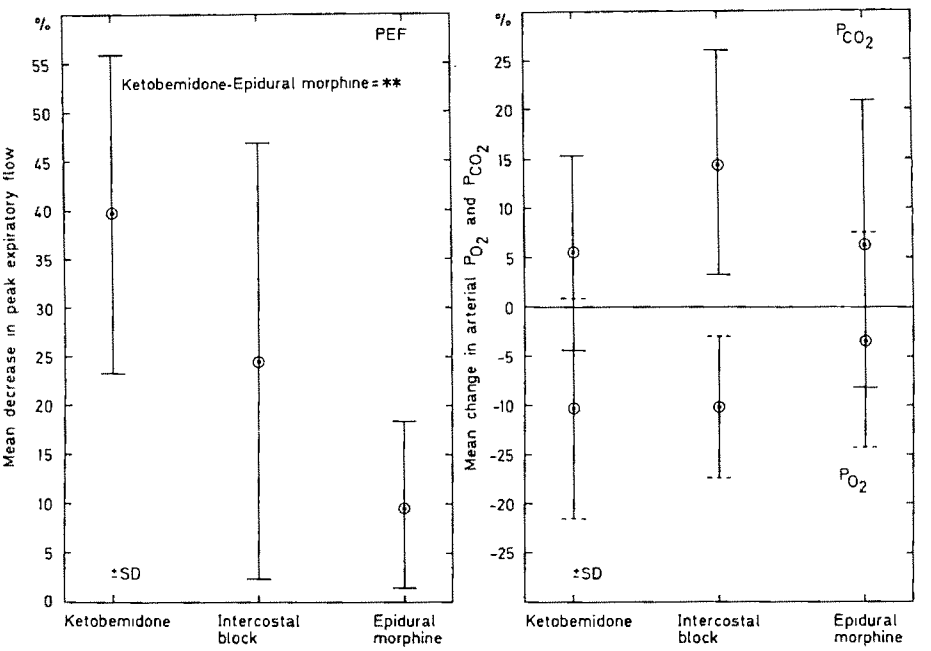


FIG 2. Postoperative percentage changes in peak expiratory flow, Pa_{O_2}, and Pa_{CO_2} (1 kPa = 7.5 mm Hg). Probability levels: **, $p \leq 0.01$.

TABLE 3

Preoperative and Postoperative Peak Expiratory Flow (PEF) and Arterial Blood Gas Tensions*

	PEF		Arterial P_{O_2}		Arterial P_{CO_2}	
	Before surgery	After surgery	Before surgery	After surgery	Before surgery	After surgery
	L/min		*mm Hg*		*mm Hg*	
Ketobemidone (group I)	398 ± 69	225 ± 51	96.7 ± 12.8	85.5 ± 9.0	36.0 ± 2.2	41.1 ± 3.0
	$p < 0.001$		$p < 0.02$		$p < 0.001$	
Intercostal block (group II)	371 ± 64	276 ± 102	96.7 ± 6.7	86.2 ± 4.5	35.2 ± 2.2	37.5 ± 3.7
	$p < 0.01$		$p < 0.001$		NS	
Epidural morphine (group III)	401 ± 105	359 ± 107	94.5 ± 14.5	90.0 ± 9.0	36.0 ± 3.7	37.5 ± 6.0
	$p < 0.01$		NS		NS	

* Values are means ± SD.

monary complications in the form of atelectasis and pneumonia. Vomiting was 4 times more frequent after intramuscular ketobemidone than after epidural morphine.

Plasma concentrations of morphine and its analgesic effects are highly variable after intramuscular injection of morphine (7). Patient-controlled analgesia with small intravenous doses of narcotic analgesic delivered repeatedly on demand and controlled by the patient (4, 11) would appear to be more logical than intramuscular injections from both pharmacokinetic and pharmacodynamic points of view because of the marked individual variations in pharmacokinetics and pain sensitivity. However, in its present form, the technique of patient-controlled injection of morphine on demand is impractical for routine use in surgical wards and most of the disadvantages of therapy with narcotic analgesics still remain (11).

Intercostal nerve blocks give analgesia of long duration without the drowsiness or respiratory depression associated with intramuscular narcotics. The analgesia, however, does not last long enough and it is generally necessary to repeat the blocks. In our study, the mean duration with intercostal block with bupivacaine was 11 hours, and all patients in group II required additional intramuscular narcotic analgesia. The postoperative PEF values were higher in our patients following intercostal blocks than they were

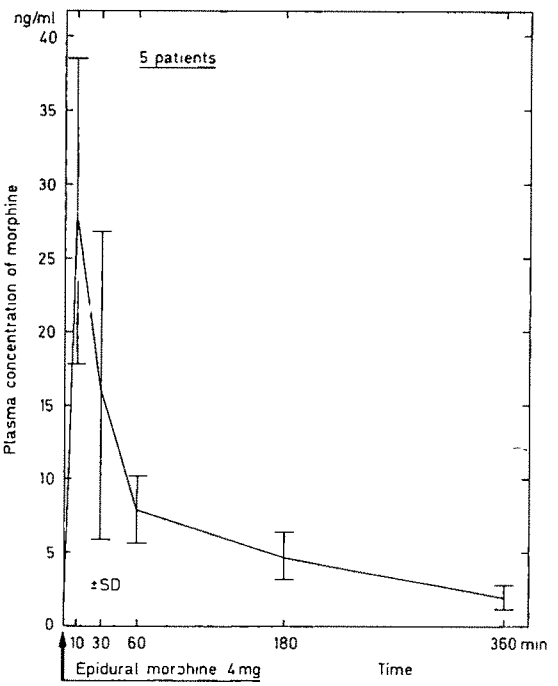


FIG 3. Plasma levels after 4 mg of epidural morphine.

following intramuscular ketobemidone (Table 3), as reported by others (9, 13). Repeated intercostal blocks, which eliminate the need for an intramuscular narcotic, would probably have reduced the incidence of vomiting and urinary retention. However, repeat blocks involve discomfort for the patient and are time consuming for the anesthesiologist (9); they also involve, of course, increased risk of pneumothorax. The reported incidence of this complication varies from 0.1% to 19% (13); in our study there was one case.

Epidural morphine proved to be superior to the other two methods of relieving postoperative pain. In 40% of the patients in group III, a single injection gave complete pain relief; in the remaining 60%, the duration of analgesia was considerably longer than with either of the other two methods. Nearly 90% of patients found epidural morphine to give excellent analgesia; only 6% were dissatisfied.

Changes in postoperative Pa_{O_2} and Pa_{CO_2}, as well as the postoperative reduction of PEF, were least marked in group III. Although no final conclusions can be drawn from the present observations, as patients given epidural morphine had more normal postoperative PEF and arterial blood gas values, it would appear that patients with compromised preoperative respiratory function might particularly benefit if postoperative analgesia were provided by epidural morphine rather than by intercostal blocks or intramuscular narcotics (Table 3).

The early appearance of morphine in plasma following injection into the epidural space suggests a rapid intravascular uptake from the site of injection (6, 14). The initial plasma morphine levels after epidural injection were relatively high and might have had systemic effects. However, the plasma morphine levels after 30 minutes were low, which, in view of the 3-hour half-life of morphine and long duration of analgesia associated with epidural morphine, strongly supports the concept that the analgesic effects of epidurally injected narcotics are due to a local action on the spinal cord.

The long duration of analgesia could be explained by two mechanisms. First, by prolonged elevation of morphine concentration in the vicinity of spinal cord opiate receptors due to the locally high concentration of morphine in the epidural space. Second, the duration of analgesia might also be related to the primary drug-receptor interaction and binding of receptor sites. This receptor binding may be prolonged due to slow reversal, i.e., giving long duration of analgesia which declines more slowly than would be expected from morphine levels in plasma or cerebrospinal fluid.

Isolated cases of delayed respiratory depression after relatively large doses of epidural narcotics have been reported, mostly in older, poor risk patients undergoing major surgery with associated large blood loss and acute or chronic respiratory insufficiency (15–17). We saw no delayed respiratory depression in our patients but, in view of the known sensitivity to narcotics, we have modified our technique for elderly, high risk patients and now insert a preoperative epidural catheter with its tip near T7–8 or T8–9 and use only 2-mg doses of morphine (18). In a previous study of 280 patients (6), and in another 300 patients receiving epidural morphine for postoperative pain relief, we did not encounter any delayed respiratory depression with doses of 2 to 4 mg of epidural morphine. However, patients, particularly the frail and elderly, should be observed for delayed respiratory depression until more is known about this potentially dangerous complication.

ACKNOWLEDGMENTS

The authors are grateful for the research and clerical contributions of Ulf Borg, Research Engineer; Ing-Marie Ackheim, Administrative Secretary; and Kathy Angell, Senior Secretary.

REFERENCES

1. Wallace PGM, Norris W. The management of postoperative pain. Br J Anaesth 1975;47:113–20.
2. Pflug AE, Bonica JJ. Physiopathology and control of postoperative pain. Arch Surg 1977;112:773–81.

3. Attitude to pain. Editorial. Br Med J 1975;3:261.
4. Tamsen A. Patient controlled analgesic therapy. The pharmacokinetics of 3 opiate analgesics in surgical patients and their relation between postoperative demand for analgesics and individual levels of endorphines and substance P in cerebrospinal fluid, dissertation, Uppsala Universty, 1981.
5. Edlund PO. Determination of opiates in biological samples by glass capillary gas chromatography with electron capture detection. J Chromatogr 1981;206:109–16.
6. Rawal N, Sjöstrand U, Dahlström B. Postoperative pain relief by epidural morphine. Anesth Analg 1981;60:726–31.
7. Austin KL, Stapleton JV, Mather LE. Relationships between blood meperidine concentrations and analgesic response. Anesthesiology 1980;53:460–6.
8. Nunn JF, Slavin G. Posterior intercostal nerve block for pain relief after cholecystectomy. Br J Anaesth 1980;52:253–9.
9. Engberg G. Single dose intercostal nerve blocks with etidocaine for pain relief after upper abdominal surgery. Acta Anaesthesiol Scand (Suppl) 1975;60:43–9.
10. Utting JE, Smith JM. Postoperative analgesia. Anaesthesia 1979;34:320–2.
11. Hug CC. Improving analgesic therapy. Anesthesiology 1980;53: 441–3.
12. Holmdahl M H:son, Modig J. The role of regional block versus parenteral analgesics in patient management with special emphasis on the treatment of postoperative pain. Br J Anaesth 1975;47:264–70.
13. Moore DC. Intercostal nerve block for postoperative somatic pain following surgery of thorax and upper abdomen. Br J Anaesth 1975;47:284–8.
14. Weddel SJ, Ritter RR. Serum levels following epidural administration of morphine and correlation with relief of postsurgical pain. Anesthesiology 1981;54:210–4.
15. Cousins MJ, Mather LE, Glynn CJ, et al. Selective spinal analgesia. Lancet 1979;1:1141–2.
16. Modig J. Postoperative analgesia with epidural morphine (Swedish). Acta Soc Med Suecanae 1980;89:51(AN 29).
17. Scott DB, McClure J. Selective epidural analgesia. Lancet 1979;1:1410–1.
18. Berkowitz BA, Ngai SH, Yang JC, et al. The disposition of morphine in surgical patients. Clin Pharmacol Ther 1975;17: 629–35.

Assessment of Beta Blockade with Propranolol

Each of seven healthy subjects received, on a weekly basis, placebo or 10, 20, 40, 80, or 160 mg of propranolol orally four times daily. The subjects' ages ranged from 22 to 28 years. The effect of propranolol on the resting heart rate and the heart rate response to the Valsalva maneuver, tilt, isoproterenol, and maximal exercise were measured. Coefficients of determination were calculated from the individual dose-response curves. The results indicate that the resting heart rate and the tachycardiac response to the Valsalva maneuver and tilt cannot be used to estimate beta blockade. Propranolol concentrations correlated well (mean $r^2 = 0.80$) with the isoproterenol dose ratio minus one, but isoproterenol challenges appear clinically inapplicable. Reduction in maximal exercise tachycardia correlated best with propranolol concentrations (mean $r^2 = 0.89$) but, to the extent that exercise could not be performed there was no reliable way of clinically documenting beta blockade and only the serum concentration of propranolol was available as an indicator of appropriate therapy. (*Hager WD, Pieniaszek HJ Jr, Perrier D, Mayersohn M, Goldberger V: Assessment of beta blockage with propranolol. Clin Pharmacol Ther 1981;30:283–90*)

ANESTH ANALG
1982;61:99-103

Cardiovascular Changes during Sodium Nitroprusside or Adenosine Triphosphate Infusion in the Rat

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With the technical assistance of Susan Anderson

HOFFMAN, W. E., SATINOVER, I., MILETICH, D. J., ALBRECHT, R. F., AND GANS, B. J.: Cardiovascular changes during sodium nitroprusside on adenosine triphosphate infusion in the rat. Anesth Analg 1982;61:99-103.

The purpose of these experiments was to compare the cardiovascular and regional hemodynamic effects of two hypotensive drugs, sodium nitroprusside (SNP) and adenosine triphosphate (ATP). Rats anesthetized with halothane were studied under control conditions and during hypotension of 65 and 40 torr induced with intravenous SNP (group 1) or ATP (group 2). Cardiac output and regional hemodynamic changes were measured with radioactive microspheres. A third group of control rats received sham infusions without SNP or ATP. SNP-induced hypotension was associated with no significant changes in heart rate or cardiac output. Hypotension induced with ATP was associated with a significant decrease in heart rate and a significant increase in cardiac output. Cerebral blood flow did not change at mean pressure levels of 65 or 40 torr with either SNP or ATP. Both renal and skin blood flow decreased significantly during SNP- and ATP-induced hypotension. Hypotension induced with SNP and ATP significantly increased skeletal muscle blood flow compared with saline control treatment. These changes were greater in rats treated with SNP than in rats treated with ATP. Differences between SNP and ATP were also observed in myocardial blood flow. Intravenous ATP infusion resulted in 200% to 300% increases in myocardial blood flow whereas SNP produced no significant change. The results indicate that compared with SNP, ATP has certain advantages for the induction of hypotension. These include an absence of tachyphylaxis during hypotensive anesthesia and the ability to maintain a constant level of blood pressure by titrating the ATP dose. Major differences between the two drugs were apparent in skeletal muscle, where SNP was a more potent vasodilator, and in the heart, where ATP was associated with large increases in myocardial blood flow.

Key Words: ANESTHETIC TECHNIQUES: hypotensive, adenosine triphosphate and nitroprusside.

HYPOTENSIVE anesthesia is used during surgery to decrease blood loss and to produce a drier surgical field. Sodium nitroprusside (SNP) has been used most often for hypotensive anesthesia. However, SNP has undesirable side effects, including tachyphylaxis and cyanide toxicity (1). Adenosine triphosphate (ATP) has been suggested as an alternative to SNP as a hypotensive agent and is currently used clinically in Japan (2). The purpose of these experiments was to compare the cardiovascular and regional hemodynamic changes produced by SNP and ATP in the rat using radioactive microspheres.

Methods

Male Sprague-Dawley rats, 6 to 8 months old, weighing 400 to 500 g each were used in these experiments. Rats were anesthetized with halothane and a tracheostomy was performed for mechanical ventilation with 1% halothane in 100% O_2 using a Harvard small animal respirator. PE50 catheters filled with heparinized saline were inserted into the right femoral artery and vein and into the left ventricle via the right carotid artery. Pressure pulses were monitored using a Hewlett-Packard pressure transducer and chart recorder to ensure correct placement of the left ventricular catheter. Following completion of surgery the

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This work was supported by National Institutes of Health grant HL25399 and Research Career Development Award HL/AG 00672 to W.E.H.

Received from the Departments of Anesthesiology and Oral Maxillofacial Surgery, Michael Reese Hospital and Medial Center, Chicago, Illinois. Accepted for publication September 28, 1981.

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inspired halothane concentration was decreased to 0.5% in 100% O_2 and the rats were allowed to stabilize for 30 minutes. During this time arterial P_{CO_2} was adjusted to 35 to 40 torr by altering the ventilation rate. Rectal temperature was monitored with a Yellow Springs thermoprobe and maintained at 37 C with overhead heat lamps.

Microspheres

Each rat in these experiments was given three microsphere injections. Each microsphere injection was given under control conditions or during either SNP- or ATP-induced hypotension. The methods used for microsphere injections have been described previously (3). The microsphere labels used were cobalt-57, ruthenium-103, and scandium-46 (New England Nuclear). Microspheres were suspended in isotonic saline in a concentration of 500,000 microspheres per milliliter with 0.01% Tween-80. Stock solutions for each microsphere containing 10 to 20 ml were mixed using a vortex for 1 minute, 0.2 ml of microsphere solution containing 100,000 microspheres was withdrawn, injected into the left ventricle, and flushed in with 0.2 ml of isotonic saline. Starting before each microsphere injection and continuing 45 seconds after the end of the microsphere injection, an arterial blood sample was withdrawn from the femoral artery at a rate of 0.4 ml/min using a Harvard infusion-withdrawal pump. Separate microsphere samples were withdrawn in triplicate from each microsphere stock solution to determine the total activity of each microsphere injected. When all microsphere injections were completed in each rat, the animal was killed and the following organs dissected out and placed in 10% formalin: brain, heart, kidneys, forelimb skeletal muscle, small intestine, and skin. The following day the tissue samples were blotted dry and weighed. The net activity of each microsphere was analyzed in tissue and blood samples using a Nuclear Chicago 1035 gamma counter and a Nuclear Chicago 600 multichannel analyzer. Tissue blood flow and cardiac output were calculated according to previously described reports using an Interdata computer (3, 4).

Hypotension

Three groups of rats were tested in these experiments. Hypotension was induced with intravenous SNP infusion in one group (N = 16) and ATP in one group (N = 13), and the third group (N = 13) received saline infusions in the absence of drug-induced hypotension. The first microsphere test in each group was given under control anesthetized conditions as described above. In SNP- and ATP-treated rats the second and third microsphere tests were given after 10-minute hypotensive periods, when mean blood pressure was lowered to 65 torr (second test) and 40 torr (third test), respectively. Twenty-minute recovery periods were allowed between each hypotensive test procedure. During this time the blood pressure of each rat returned to within 10% of the original control pressure. SNP was dissolved in isotonic saline in a concentration of 0.2 mg/ml and infused in a light-free environment. ATP was dissolved in a Krebs-Henseleit solution adjusted to a pH of 7.4 (5). Control rats received the first microsphere injection before starting an intravenous infusion and the second and third injections during infusion of isotonic saline at a rate comparable to those used for infusion of SNP and ATP. The stabilization period between each test procedure was 20 minutes for all three groups. Arterial blood microsamples were withdrawn after each microsphere test to measure blood gas tensions and pH.

All data are reported as means ± SE. Tissue blood flow changes during SNP, ATP, and vehicle treatments are reported as percent change from the first control treatment in each rat. Statistical comparisons were performed with a treatment by groups linear model analysis of variance, a paired *t*-test, measuring the change from control treatment with each test variable, and with unpaired *t*-tests comparing hypotensive drug to vehicle control treatment group at each test level.

Results

All of the 26 rats given intravenous ATP or saline successfully completed each of the three microsphere tests. The infusion rates of ATP required to induce mean blood pressure levels of 65 and 50 torr are shown in Fig 1. The level of blood pressure was easily controlled by titrating the ATP dose and there was no indication of tachyphylaxis during the hypotensive period. Of the 16 rats tested with SNP 11 successfully completed all three microsphere tests. Doses of SNP required for each hypotensive level are shown in Fig 1. Five rats completed the first and second microsphere test, but a blood pressure of 40 torr could not be attained in these rats even when the SNP infusion rate was increased to more than 400 μg/kg/min. Tachyphylaxis was considered present in these rats and they were excluded from the study. Arterial blood gas tensions and pH are shown in the Table. Blood gas tensions remained stable in all three groups

throughout the three microsphere injections. Arterial pH decreased significantly in rats given SNP and ATP at hypotensive levels of 40 torr.

Cardiovascular responses during intravenous SNP, ATP, and saline are shown in Fig 2. Saline infusion resulted in no significant change in blood pressure, cardiac output, heart rate, or total peripheral resistance during the three microsphere injections. Decreasing mean blood pressure to 65 and then to 40 torr with SNP for the second and third injections of microsphere resulted in no significant change in cardiac output or heart rate, whereas total peripheral resistance decreased significantly. ATP infusion resulted in a significant decrease in heart rate and total peripheral resistance compared with values in saline-treated control rats and a significant increase in cardiac output.

Percent changes in regional blood flows during ATP- and SNP-induced hypotension are shown in Figs 3 and 4. In control rats skeletal muscle blood flow decreased significantly at the third microsphere test, compared with values at the first control test. Blood flow in other tissues did not significantly change over the three microsphere tests in control rats. Cerebral blood flow did not significantly change during either SNP- or ATP-induced hypotension. Myocardial blood flow increased 200% to 300% during ATP-induced hypotension but did not significantly change with SNP. Renal and skin blood flow decreased in a similar manner during both SNP and

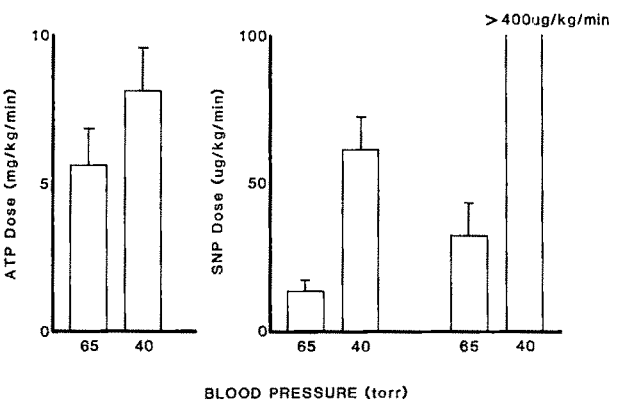


FIG 1. Adenosine triphosphate (AT) and sodium nitroprusside (SNP) doses required to produce mean blood pressure levels of 65 and 40 torr. Control blood pressures are presented in Table 1. Data for ATP infusions represent 13 rats. Data on left for SNP represent 11 rats in which hypotensive levels of 65 and 40 torr were attained with SNP less than 400 μg/kg/min. On the right are data in five rats in which a mean pressure of 40 torr could not be attained even with intravenous infusions greater than 400 μg/kg/min.

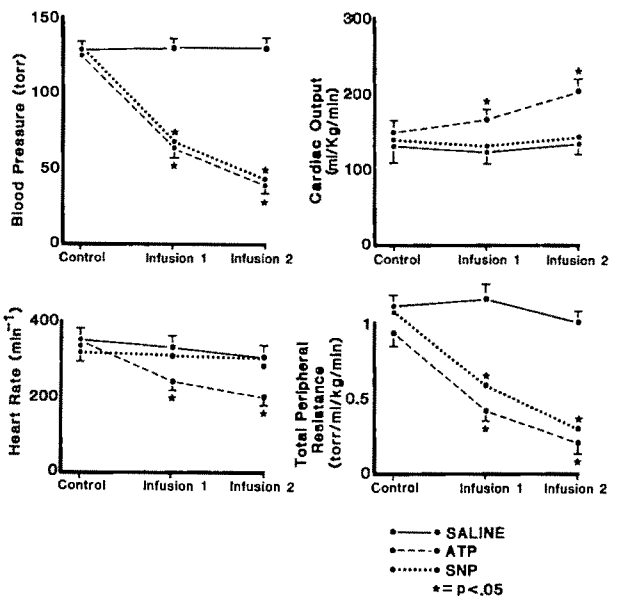


FIG 2. Cardiovascular changes with intravenous SNP, ATP, and saline control infusions. Significance values represent differences from saline control animals during each infusion period. Analyses of variance indicated a significant effect on SNP and ATP in decreasing blood pressure and total peripheral resistance compared with values for saline control infusions. ATP also produced a significant increase in cardiac output and a decrease in heart rate. Saline control treatments produced no significant change in these variables.

TABLE

Arterial Blood Gas Tensions and pH during Sodium Nitroprusside (SNP)- and Adenosine Triphosphate (ATP)-Induced Hypotension and in Control Animals

	Saline control rats (n = 13)			SNP (n = 11)			ATP (n = 13)		
	1	2	3	1	2	3	1	2	3
Arterial P_{CO_2} (torr)	38 ± 1	38 ± 1	40 ± 1	39 ± 1	39 ± 1	39 ± 1	39 ± 1	38 ± 1	39 ± 1
Arterial P_{O_2} (torr)	348 ± 17	292 ± 23	293 ± 27	239 ± 29	234 ± 27	247 ± 27	319 ± 14	318 ± 13	316 ± 11
Arterial pH	7.43 ± 0.02	7.43 ± 0.02	7.40 ± 0.02	7.41 ± 0.01	7.39 ± 0.01	7.37 ± 0.02*	7.38 ± 0.02	7.38 ± 0.01	7.34 ± 0.02*
Mean arterial blood pressure (torr)	130 ± 6	131 ± 5	128 ± 5	132 ± 4	66 ± 1*	40 ± 2*	129 ± 5	65 ± 1*	41 ± 1*

* $p < 0.05$ compared with saline control rats.

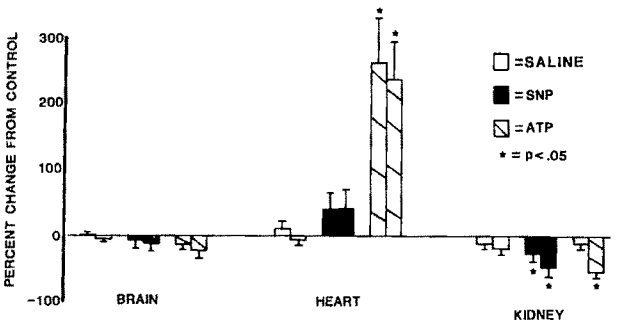


FIG 3. Brain, heart, and renal blood flow during infusion of SNP, ATP, or saline. Data for each group presented as percent change from first (control) microsphere test given to each rat. First bar graph for each group represents values for second microsphere injection in each rat, at a blood pressure of 65 torr in rats given SNP and ATP. Second bar graph for each group represents values for third microsphere injection, at a blood pressure level of 40 torr for SNP- and ATP-treated rats. Significance values represent change from control (first test) in each group. Analyses of variance indicated significant treatment effect of SNP and ATP in decreasing renal blood flow ($p < 0.05$). Myocardial blood flow increased with ATP-induced hypotension but not with SNP-induced hypotension. Repeated saline control treatments had no significant effect on flow in any region.

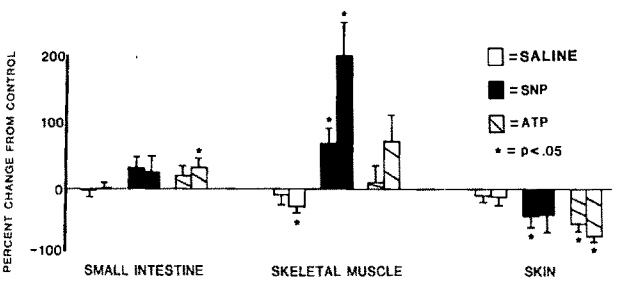


FIG 4. Small intestine, skeletal muscle, and skin blood flow during infusions of SNP, ATP, and saline. Order of treatment and significance values are as indicated in Fig 3. By analysis of variance, both SNP and ATP produced significant decreases in skin blood flow, compared with saline control treatments ($p < 0.05$). Skeletal muscle blood flow was increased with SNP and ATP treatment, compared with values in saline-treated control rats ($p < 0.05$), and this increase was greater with SNP-induced hypotension than with ATP-induced hypotension. ATP produced significant increases in small intestine blood flow compared with values for saline control treatments, but these changes were not different from values for SNP treatment.

ATP hypotensive periods. Skeletal muscle blood flow increased significantly during SNP-induced hypotension but did not significantly change during ATP infusion, but both treatments were different from saline control treatments, as analyzed by analysis of variance ($p < 0.05$). The increase in skeletal muscle blood flow was significantly greater in SNP- than in ATP-treated rats.

Discussion

In these experiments, ATP-induced hypotension was accomplished with no indication of tachyphylaxis. This contrasts with reports of tachyphylaxis observed during SNP infusion (1, 6) and with the tachyphylaxis seen here during hypotension induced with SNP. The cardiovascular changes that occurred in the present study during ATP infusion were different from those observed with SNP. Hypotension produced by ATP infusion was accompanied by a significant decrease in heart rate and an increase in cardiac output, whereas neither of these variables changed significantly with SNP. Regional hemodynamic changes during SNP- and ATP-induced hypotension were similar except in skeletal muscle and heart tissue. In skeletal muscle, both SNP and ATP increased blood flow, compared with values in saline-treated control rats, but these changes were greater during SNP than ATP infusion. In the myocardium, ATP produced large and statistically significant increases in blood flow during the hypotensive state. In contrast, SNP-induced hypotension produced no significant change in myocardial blood flow. The absence of tachyphylaxis during ATP infusion and the maintenance of vital organ blood flow at blood pressure levels approximately 30% of control values suggest that compared with SNP, ATP may be a safe hypotensive drug with certain advantages.

The mechanism of action of intravascular ATP has been studied by several investigators. As ATP is rapidly metabolized in whole blood, it is assumed that a significant portion of its cardiovascular effects are the result of vasoactive metabolites such as adenosine (7). However, Forrester et al (5) and Winbury et al. (8) have reported that intravascular ATP is a more potent vasodilator than an equimolar concentration of adenosine in brain and heart tissue, respectively, suggesting that the direct vascular effects of ATP may play an important role in the cardiovascular changes observed. It has been reported (9, 10) that both ATP and adenosine produce peripheral vasodilation by direct effects on vascular smooth muscle and by inhibition of the sympathetic nervous system. Inhibition of vasoconstriction produced by sympathetic nervous stimulation is produced by inhibition of norepinephrine release by both ATP and adenosine (11–13).

The cardiovascular and regional hemodynamic changes produced during SNP-induced hypotension are consistent with previous reports. Cardiac output does not increase during SNP infusion, primarily because of the effect of SNP on central venous pressure and venous return (14, 15). SNP increases hind limb blood flow, whereas it has little effect on myocardial blood flow (14). It has been suggested that SNP has direct cerebrovasodilating effects which al-

low maintenance of cerebral blood flow at control levels at much lower levels of hypotension than is possible with ganglionic blockade (16).

Although the mechanism by which ATP alters heart rate is undefined, the effects of ATP on the sympathetic nervous system have been implicated (17). Rowe et al (18) reports that the infusion of ATP increased cardiac output, myocardial oxygen demand, and coronary blood flow. The increase in coronary blood flow was greater than necessary (an increase of more than 500%) to compensate for the increase in O_2 demand. This is supported by the work of Wolf and Berne (19). Winbury et al (7) also reported coronary vasodilation with ATP, a vasodilation that was 5 times greater than that seen with adenosine. ATP has been reported to have direct cerebrovasodilating effects in the cat and the baboon (5), and Maruno et al (2) found that both ATP and SNP, but not trimethaphan, were able to maintain cerebral blood flow when blood pressure was decreased to 50% of control values.

These studies indicate that ATP, like SNP, has a rapid onset of action during the induction of hypotension and that blood pressure recovers quickly when the infusion is terminated. The hypotensive level is easy to maintain by titrating the infusion rate of ATP and tachyphylaxis does not appear to be a problem. ATP-induced hypotension is marked by a significant decrease in heart rate and a significant increase in cardiac output. Although most regional vascular changes are similar with ATP and SNP during hypotensive anesthesia, SNP infusion produces a greater increase in skeletal muscle blood flow, whereas ATP produces greater increases in myocardial tissue blood flow. The ability of ATP to maintain vital organ blood flow during hypotensive anesthesia and the absence of both tachyphylaxis and risk of cyanide toxicity are advantages in the consideration of this drug as a hypotensive agent in clinical practice.

ACKNOWLEDGMENT

We wish to thank Alberta Morgan for the preparation of this manuscript.

REFERENCES

1. Tinker JH, Michenfelder JD. Sodium nitroprusside: pharmacology, toxicology and therapeutics. Anesthesiology 1976;45: 340–54.
2. Maruno Y, Hashimoto Y, Saito N, Okazaki N, Fuji A, Aono M. The effects of 50% hypotension induced by ATP, sodium nitroprusside and trimethaphan on canine cerebral blood flow and metabolism. Masui 1978;27:1527–32.
3. Hoffman WE, Miletich DJ, Albrecht RF. Repeated microsphere injections in rats. Life Sciences 1981;28:2167–72.
4. Heymann MA, Payne BD, Hoffman JIE, Rudolph AM. Blood flow measurements with radionuclide-labelled particles. Prog Cardiovasc Dis 1977;20:55–62.
5. Forrester T, Harper AM, MacKenzie ET, Thomas E. Effect of adenosine triphosphate and some derivatives on cerebral blood flow and metabolism. J Physiol 1979;296:343–55.
6. Pagani M, Vatner SF, Braunwald E. Hemodynamic effects of intravenous sodium nitroprusside in the conscious dog. Circulation 1978;57:144–51.
7. Jorgensen S. Breakdown of adenine and hypoxanthine nucleotides and nucleosides in human plasma. Acta Pharmacol Toxicol 1956;12:294–302.
8. Winbury MM, Papierski DH, Hemmer ML, Hambourger WE. Coronary dilator action of the adenine-ATP series. J Pharmacol Exp Ther 1953;109:255–60.
9. Su C. Purinergic inhibition of adrenergic transmission in rabbit blood vessels. J Pharmacol Exp Ther 1978;204:351–61.
10. Kamikawa Y, Cline WH, Su C. Diminished purinergic modulation of the vascular adrenergic neurotransmission in spontaneously hypertensive rats. Eur J Pharmacol 1980;66:347–53.
11. Wakade AR, Wakade TD. Inhibition of norepinephrine release by adenosine. J Physiol (Lond) 1978;282:35–49.
12. Verhaeghe RH, Vanhoutte PM, Shepherd JT. Inhibition of sympathetic neurotransmission in canine blood vessels by adenosine and adenine nucleotides. Circ Res 1977;40:208–15.
13. Enero MA, Saidman BQ. Possible feed-back inhibition of noradrenaline release by purine compounds. Nauyn-Schmiedelbergs Arch Pharmacol 1977;297:39–46.
14. Wang HH, Liu LMP, Katz RL. A comparison of the cardiovascular effects of sodium nitroprusside and trimethaphan. Anesthesiology 1977;46:40–8.
15. Pouleur H, Covell JW, Ross J. Effects of nitroprusside on venous return and central blood volume in the absence and presence of heart failure. Circulation 1980;61:328–37.
16. Stoyka WW, Schutz H. The cerebral responses to sodium nitroprusside and trimethaphan controlled hypotension. Can Anaesth Soc J 1975;22:275–83.
17. Emmelin N, Feldberg W. Systemic effects of adenosine triphosphate. Br J Pharmacol 1948;3:273–84.
18. Rowe GG, Afonso S, Gurtner HP, et al. Systemic and coronary hemodynamic effects of adenosine triphosphate and adenosine. Am Heart J 1962;64:228–34.
19. Wolf MM, Berne RM. Coronary vasodilator properties of purine and pyrimidine derivatives. Circ Res 1956;4:343–8.

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1982;61:104-8

Pharmacokinetics of Etidocaine in Fetal and Neonatal Lambs and Adult Sheep

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PEDERSEN, H., MORISHIMA, H. O., FINSTER, M., ARTHUR, G. R., AND COVINO, B. G.: Pharmacokinetics of etidocaine in fetal and neonatal lambs and adult sheep. Anesth Analg 1982;61:104-8.

Etidocaine, 2.5 mg/kg, was injected intravenously into either a nonpregnant adult sheep (N = 7), neonatal lamb (N = 7), or fetal lamb (N = 6), all with catheters in the femoral vessels and urinary bladders. Serial arterial blood and urine samples were obtained over 4 hours and analyzed for unchanged etidocaine using a gas chromatographic technique. The distribution and elimination half-lives of etidocaine in the blood of nonpregnant adults and newborn sheep were similar. The volume of distribution was significantly greater in the newborn (4.64 L/kg) compared with the adult (1.52 L/kg) as was the total body clearance (87.4 vs 30.3 ml/min/kg). Renal clearance was also significantly greater in the newborn. The data indicate that the newborn lamb is capable of eliminating etidocaine as rapidly as the adult. Following injection of the drug into the fetus, fetal blood concentrations became undetectable after 30 minutes due to placental transfer into the maternal compartment.

Key Words: ANESTHETICS, Local: etidocaine; PHARMACOKINETICS: etidocaine; ANESTHESIA: obstetric.

MINIMAL information is available concerning the pharmacokinetics of local anesthetics in the fetus and neonate. Recently, two studies have been reported on the comparative pharmacokinetics of lidocaine in fetal, neonatal, and adult sheep (1) and in neonatal and adult humans (2). Although the absolute values for the various pharmacokinetic parameters differed between sheep and man, the relative differences between neonates and adults were quite similar. Both studies demonstrated that the half-life of lidocaine was longer in neonates than in adults due to greater volume of distribution in the former. Total body clearance of lidocaine was also greater in neonates, mainly due to increased renal clearance. No difference in hepatic clearance of lidocaine existed between the neonate and the adult, suggesting that the neonate is capable of metabolizing the drug to the same extent as the adult. The metabolism of local anesthetics by the human newborn has also been demonstrated by other investigators (3-5).

Based on the results obtained with lidocaine, it would appear that the sheep can serve as an appropriate model for pharmacokinetic studies of other local anesthetics. The current investigation was initiated to compare the pharmacokinetics of etidocaine in nonpregnant adult sheep and in neonatal and fetal lambs. This agent is similar to lidocaine in terms of chemical structure, but differs markedly in physicochemical properties, such as protein-binding and lipid solubility (6). Several studies (7, 8) have been performed on the pharmacokinetics of etidocaine in adult man. However, only limited data are available on the rate of disappearance of etidocaine from blood and on the rate of metabolism of etidocaine in neonates (9).

Methods and Materials

Seven nonpregnant adult ewes, seven newborn lambs, and six fetuses and their mothers were studied.

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Supported in part by grant 5P50-GM09069, National Institute of General Medical Sciences, National Institutes of Health.

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The newborns had been delivered vaginally at term, 1 to 5 days (average, 2½ days) before the study. Gestational ages of the fetuses ranged from 125 to 136 days (average 130 days).

The operative procedure for placement of catheters in the adult, newborn, and fetus was similar to that described previously (1). In nonpregnant ewes and newborn lambs, catheters were placed in the femoral artery and vein under local anesthesia using procaine. In the nonpregnant ewes and most of the newborn lambs, the urinary bladder was cannulated through the urethra, but in some of the latter, via suprapubic incision. The fetal preparation involved a hysterotomy performed under spinal anesthesia with tetracaine hydrochloride (6 to 9 mg). The fetal end of the umbilical cord was partially exposed and the urachus cannulated with a polyethylene catheter, the tip of which was advanced into the bladder. A fetal femoral artery and vein were also catheterized through a separate uterine incision. A polyethylene catheter was introduced into the amniotic cavity and the uterine and abdominal walls were closed. Maternal femoral artery and vein were also cannulated. All intrauterine studies were performed at least 7 days (range, 7 to 32 days) after the operation to allow for adequate recovery of renal function in the fetus.

Each study was preceded by a control period of 2 hours during which the cardiovascular and acid-base state of the nonpregnant adult, newborn, or fetal lamb was found to be within normal limits (10) (Table 1). Thereafter, 0.5% etidocaine hydrochloride, 2.5 mg/kg, was injected over a period of 60 seconds into the femoral vein of the nonpregnant adult ewe, newborn, or fetal lamb. Weight of the fetus was estimated on the basis of a composite curve of average weights of fetal lambs in relation to gestational age, prepared from two reported studies (11, 12) and verified after the experiment. All animals were monitored during the control period and for 4 hours after injection of the drug. Arterial blood pressure and heart rate were recorded continuously on a polygraph. Samples of arterial blood (1.0 ml each) were obtained at predetermined intervals from 1 minute to 4 hours after the injection (Table 2). In addition, in fetal studies, a sample of amniotic fluid was withdrawn simultaneously with the maternal and fetal blood samples. In all studies, specimens of urine were collected at 5 minutes and thereafter simultaneously with blood samples up to 240 minutes. Blood samples were analyzed for pH, P_{CO_2}, and P_{O_2}; urine and amniotic fluid were analyzed for pH alone, using Radiometer microelectrodes and a Radiometer gas analyzer. Plasma was separated by centrifugation and stored at −15 C, along with urine and amniotic fluid samples. All samples were subsequently analyzed for unchanged etidocaine

TABLE 1

Heart Rate, Blood Pressure, and Blood pH and Gas Tensions before Intravenous Administration of Etidocaine*

	Nonpregnant adult (N = 7)	Neonate (N = 7)	Fetus (N = 6)
Heart rate (beats/min)	120 ± 5	200 ± 14	168 ± 4
Mean arterial pressure (torr)	106 ± 4	80 ± 4	51 ± 5
pHa	7.47 ± 0.02	7.42 ± 0.02	7.38 ± 0.02
Pa_{CO_2} (torr)	32 ± 2	38 ± 2	45 ± 3
Pa_{O_2} (torr)	95 ± 6	82 ± 3	21 ± 3
Amniotic fluid pH			6.78 ± 0.09

* Values are means ± SE.

TABLE 2

Etidocaine Concentrations in Arterial Blood (μg/ml)*

Time	Nonpregnant adult	Neonate	Fetus	Mother
min				
1	5.28 ± 0.8†	1.62 ± 0.18‡	0.56 ± 0.15	0.29 ± 0.11
2	4.22 ± 0.52†	1.27 ± 0.16‡	0.48 ± 0.05§	0.23 ± 0.02
10	1.9 ± 0.2†	0.68 ± 0.11‡	0.18 ± 0.04	0.09 ± 0.01
15	1.37 ± 0.15†	0.5 ± 0.09‡	0.07 ± 0.02	0.09 ± 0.01
30	0.69 ± 0.11†	0.29 ± 0.06‡	0.04 ± 0.02	ND‖
60	0.33 ± 0.05†	0.15 ± 0.03	ND	ND
90	0.12 ± 0.04†	0.09 ± 0.02	ND	ND
120	0.06 ± 0.03	0.05 ± 0.05	ND	ND
180	0.08 ± 0.05	ND	ND	ND
240	0.03 ± 0.02	ND	ND	ND

* Values are means ± SE.
† Significantly different from newborn and fetal values.
‡ Significantly different from fetal values.
§ Significantly different from maternal value.
‖ ND, Not detectable.

using a gas chromatographic technique modified from that described by Keenaghan (13) for lidocaine and prilocaine. The apparatus and extraction procedures were practically the same, the only difference being the use of 2-ethyl,2(isobutylamino)-*N*-(2,6 dimethylphenyl) acetamide, an experimental lidocaine-like local anesthetic, as internal standard. The method is sensitive to ±0.01 μg/ml of etidocaine with excellent reproducibility. Pharmacokinetic analysis of the data obtained from the nonpregnant adult ewe and from the newborn was performed utilizing a two-compartment model with elimination from the central compartment (14). The rapid decline in measurable blood concentrations in the fetuses and their mothers following fetal injection precluded kinetic analysis in these two groups of animals. Furthermore, the fact that fetal blood levels depend primarily on distribution into the mother makes it inappropriate to subject fetal blood concentrations to conventional pharmacokinetic analysis. Renal clearance was calculated by dividing the amount of etidocaine excreted in the urine in 240 minutes by the area under the plasma concentration-time curve to 240 minutes.

Student's *t*-test was used to compare data from the three age groups. $p < 0.05$ was regarded as being significant.

Results

The cardiovascular and acid-base states of all animals were good before the experiment (Table 1). In the nonpregnant adult ewes, drug injection was followed by a brief period of tachycardia from 120 ± 5 (SEM) to 152 ± 11 beats per minute ($p < 0.05$). This was accompanied by hypertension from 106 ± 4 to 145 ± 6 torr mean arterial pressure ($p < 0.01$). A transient but significant ($p < 0.05$) decrease in the fetal heart rate from 168 ± 4 to 133 ± 12 beats per minute occurred within 1 minute after the end of fetal injection. It was associated with a decrease in fetal $Paco_2$ from 21 ± 3 to 18 ± 2 torr. Fetal arterial pressure remained steady. These changes in the nonpregnant adult and in the fetus lasted less than 5 minutes. The cardiovascular state and arterial oxygenation remained unaltered in newborn lambs.

The mean arterial concentrations of etidocaine in nonpregnant adults, neonates, and fetuses and their mothers at various times following intravenous injection are shown in Table 2. A peak arterial etidocaine concentration of 5.28 ± 0.8 μg/ml was observed 1 minute following injection in the nonpregnant adult compared with values of 1.62 ± 0.18 μg/ml in the newborn and 0.56 ± 0.15 μg/ml in the fetus ($p < 0.01$). The blood level of etidocaine decreased most rapidly in the fetus so that after 30 minutes no etidocaine could be detected in the fetal blood. Within 1 minute of administration of etidocaine to the fetus, 0.29 ± 0.11 μg/ml of etidocaine was measured in maternal blood; after 15 minutes the drug was no longer detectable (Fig 1).

The distribution half-life $T_{1/2\alpha}$ of etidocaine was similar in both the nonpregnant adult and the neonate, averaging 5.00 ± 0.82 minutes and 4.70 ± 0.45 minutes, respectively. The elimination half-life $T_{1/2\beta}$ values were also similar: 34.90 ± 3.75 minutes in the nonpregnant adult compared with 36.90 ± 2.69 minutes in the neonate. Thus, although concentrations of etidocaine in arterial blood were significantly different in these two groups, the rate of disappearance, in terms of both tissue redistribution and elimination, were quite similar. The volumes of distribution for the central compartment V_C and during the elimination phase $V_{D\beta}$ were significantly greater in the newborn than in nonpregnant adults (Table 3). In addi-

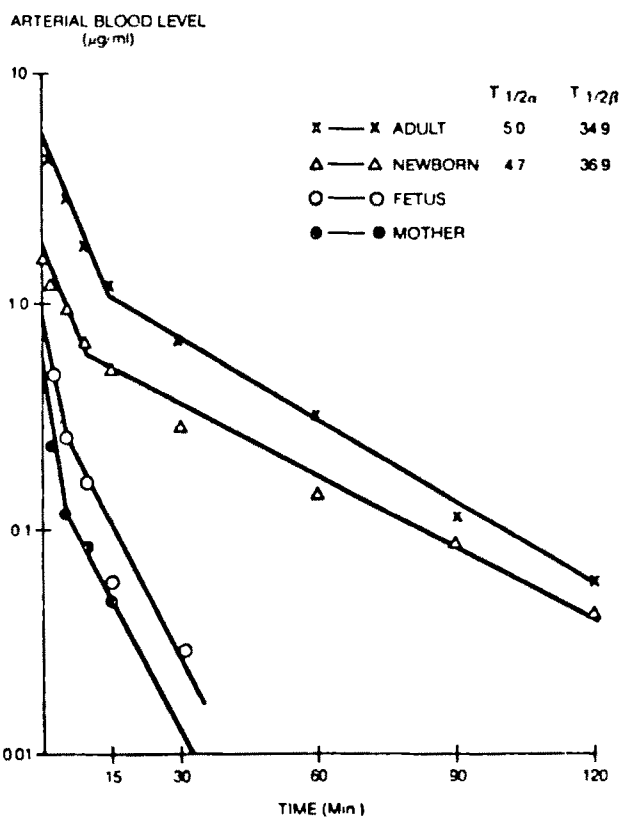


FIG 1. Etidocaine concentrations (base) in arterial blood following intravenous injection of 2.5 mg/kg given to nonpregnant adults, newborn sheep, or fetal lambs. $T_{1/2\alpha}$, Distribution half life; $T_{1/2\beta}$, elimination half-life.

tion, the total body clearance Cl_T averaged 87.40 ± 14.65 ml/min/kg in the newborn compared with 30.30 ± 4.53 ml/min/kg in the adult. Renal clearance Cl_R was also greater in the newborn, averaging 2.40 ± 1.22 ml/min/kg compared with a value of 0.22 ± 0.18 ml/min/kg in the adult.

The mean urine output before the injection of etidocaine was 0.08 ± 0.03 ml/kg/min in the nonpregnant adult, 0.14 ± 0.02 ml/kg/min in the newborn, and 0.18 ± 0.05 ml/kg/min in the fetus. It remained unchanged in all three groups throughout the experiment. So did the urinary pH, which in the control period was 6.38 ± 0.24, 5.97 ± 0.18, and 6.62 ± 0.12 in the nonpregnant adult, newborn, and fetus, respectively. Unmetabolized drug appeared in the urine of the nonpregnant adult, newborn, and fetus within 5 minutes after injection (Fig 2). Etidocaine was no longer detectable after 180 minutes in urine of nonpregnant adults or after 120 minutes in the fetal urine. The total amount of unmetabolized drug excreted in the urine was highest in the newborn, amounting to 3% of the injected dose, compared with 0.6% in the nonpregnant adult and 0.36% in the fetus ($p < 0.01$). Trace amounts of etidocaine were detected in the amniotic fluid between 2 and 60 minutes after fetal injection.

TABLE 3

Pharmacokinetic Indices of Etidocaine in Adult Sheep and Neonatal Lambs*

Indices	Nonpregnant adult	Neonate
$T_{1/2\alpha}$ (min)	5.00 ± 0.82	4.70 ± 0.45
$T_{1/2\beta}$ (min)	34.90 ± 3.75	36.90 ± 2.69
V_C (L/kg)	0.52 ± 0.11†	1.65 ± 0.21
$V_{D\beta}$ (L/kg)	1.52 ± 0.28†	4.64 ± 0.96
Cl_T (ml/min/kg)	30.30 ± 4.52†	87.40 ± 14.65
Cl_R (ml/min/kg)	0.22 ± 0.18	2.40 ± 1.22
$Cl_{hepatic}$ (ml/min/kg)	30.08	85.00

* Values are means ± SE. Abbreviations used are: $T_{1/2\alpha}$, distribution half-life; $T_{1/2\beta}$, elimination half-life; V_C, volume of distribution of drug for central compartment; $V_{D\beta}$, volume of distribution during elimination phase; Cl_T, total body clearance; Cl_R, renal clearance; $Cl_{hepatic}$, hepatic clearance.

† Significantly different from the neonatal values.

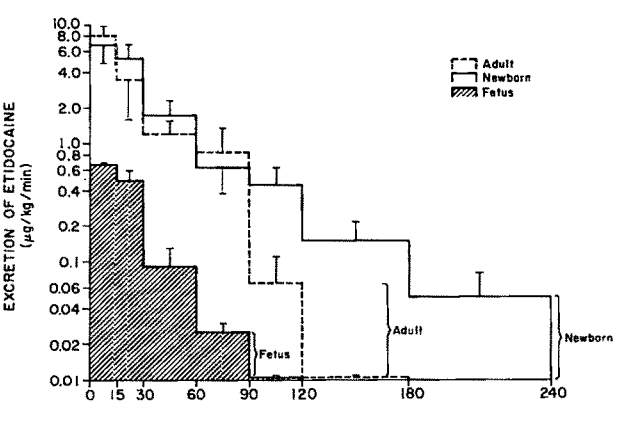


FIG 2. Comparative renal excretions of etidocaine in nonpregnant adult, newborn, and fetal sheep following intravenous administration of 2.5 mg/kg.

Discussion

The results of this study indicate that the half-life of etidocaine, i.e., rate of disappearance from blood, is similar in the nonpregnant adult sheep and in neonatal lambs. Although the half-life values were similar, the physiologic disposition and elimination of etidocaine in these two groups differ considerably. Half-life of a drug is directly related to the volume of distribution, i.e., degree of tissue uptake, and inversely related to clearance of the agent ($T_{1/2} = V_D/Cl$). Although the $T_{1/2\alpha}$ and $T_{1/2\beta}$ of etidocaine were similar in the neonate and nonpregnant adult, the volume of distribution in the neonate (4.64 L/kg) was 3 times greater than that in the adult (1.52 L/kg). Similarly, the total body clearance of etidocaine was significantly greater in the neonate (87.4 ml/min/kg) than in the adult (30.0 ml/min/kg). The greater volume of distribution in the neonate is consistent with the fact that, in this age group, a larger percentage of total body mass is made up of highly perfused organs (15). The enhanced total body clearance of etidocaine in the neonate is more difficult to explain. It is only in small part related to the greater renal clearance of etidocaine in the newborn (2.4 ml/min/kg), which in turn may be due to the lower urinary pH and higher urinary output, as well, perhaps, as to less plasma binding of etidocaine. Plasma binding of lidocaine and bupivacaine in the human neonate is approximately 50% of that in the adult (16). If one subtracts the renal clearance from total body clearance, the difference representing extrarenal clearance (presumably hepatic), then 85 ml/min/kg of etidocaine is cleared in the neonate compared with 30 ml/min/kg in the adult. This would suggest that the neonate may be more efficient in terms of metabolizing etidocaine than is the adult. Confirmation of this hypothesis would require the measurement of etidocaine metabolites.

A comparison of results obtained in this study with those of previous studies in which lidocaine was used (1) reveals qualitative similarities but quantitative differences in the various pharmacokinetics of lidocaine

TABLE 4

Comparative Pharmacokinetic Indices of Lidocaine and Etidocaine in Man and Adult Sheep*

	Lidocaine		Etidocaine	
	Man	Sheep	Man	Sheep
$T_{1/2\alpha}$ (min)	5.40†	5.00	6.00†	5.00
$T_{1/2\beta}$ (min)	96.00‡	30.90	156.00‡	34.90
V_C (L/kg)	0.12‡	0.90	0.17‡	0.52
$V_{D\beta}$ (L/kg)	1.30‡	1.84	1.90‡	1.52
Cl_T (ml/min/kg)	13.60‡	41.20	17.40‡	30.30
Cl_R (ml/min/kg)		1.01		0.22

* Abbreviations defined in footnote to Table 3.

† Values from Scott (7).

‡ Values calculated from Tucker and Mather (8) for a 70-kg man.

and etidocaine. Renal and total body clearances of lidocaine in the newborn lamb were greater than in the nonpregnant adult sheep as they were with etidocaine in the present study. In the adult sheep, the total body clearance and renal clearance of etidocaine were somewhat less than those of lidocaine. In the newborn, on the other hand, total body clearance and calculated extrarenal clearance of etidocaine were significantly greater than those of lidocaine. The rapid disappearance of etidocaine from the fetus is probably related to placental transfer of this agent into the mother. The presence of etidocaine in maternal blood within 1 minute following injection of this agent into the fetus supports this hypothesis. Similar results are seen with lidocaine (1).

Morgan and colleagues (9) investigated the disappearance rate from blood and urinary elimination of etidocaine and its metabolites in human neonates whose mothers had received etidocaine for epidural anesthesia during labor. Although the results from this study indicate a more prolonged elimination half-life of etidocaine in the human neonate (6.42 hours) than in our newborn lambs, both studies demonstrate a large volume of initial distribution and extensive clearance of etidocaine in this age group. The differences in absolute values may be related to species and methodologic differences in the two investigations.

Previous studies comparing the pharmacokinetic and metabolic properties of lidocaine and etidocaine in human adults have shown that the half-life of etidocaine is longer than that of lidocaine (7, 8), whereas the hepatic clearance and presumably metabolism of these two agents are similar (17). The greater half-life of etidocaine in adult man appears to be related to the greater volume of distribution of etidocaine (8). Table 4 shows the comparative pharmacokinetic values of etidocaine and lidocaine in adult man and sheep.

REFERENCES

1. Morishima HO, Finster M, Pedersen H, et al. Pharmacokinetics of lidocaine in fetal and neonatal lambs and adult sheep. Anesthesiology 1979;50:431–6.
2. Mihaly GW, Moore RG, Thomas J, Triggs EJ, Thomas D, Shanks CA. The pharmacokinetics and metabolism of the anilide local anaesthetics in neonates. I. Lignocaine. Eur J Clin Pharmacol 1978;13:143–52.
3. Blankenbaker WL, DiFazio CA, Berry FA Jr. Lidocaine and its metabolites in the newborn. Anesthesiology 1975;42:325–50.
4. Moore RG, Thomas J, Triggs EJ, Thomas DG, Burnard ED, Shanks CA. The pharmacokinetics and metabolism of the anilide local anaesthetics in neonates. III. Mepivacaine. Eur J Clin Pharmacol 1979;14:203–12.
5. Kuhnert BR, Knapp DR, Kuhnert PM, Prochaska AL. Maternal, fetal and neonatal metabolism of lidocaine. Clin Pharmacol Ther 1979;26:213–20.
6. Covino BG, Vassallo HG. Local anesthetics. Mechanisms of action and clinical use. New York: Grune and Stratton, 1976;8: 46–7.
7. Scott DB. Evaluation of clinical tolerance of local anaesthetic agents. Br J Anaesth 1975;47:328–31.
8. Tucker GT, Mather LE. Pharmacokinetics of local anaesthetic agents. Br J Anaesth 1975;47:213–24.
9. Morgan D, McQuillan D, Thomas J. Pharmacokinetics and metabolism of the anilide local anaesthetics in neonates. II. Etidocaine. Eur J Clin Pharmacol 1978;13:365–71.
10. Morishima HO, Heymann MA, Rudolph AM, Barrett CT, James LS. Transfer of lidocaine across the sheep placenta to the fetus. Am J Obstet Gynecol 1975;122:581–8.
11. Huggett A Stg, Widdas WF. The relationship between mammalian foetal weight and conception age. J Physiol (Lond) 1951;114:306–717.
12. Metcalfe J, Meschia G, Hellegers A, Prystowsky H, Huckabee W, Barron DH. Observations on the growth rates and organ weights of fetal sheep at altitude and sea level. Q J Exp Physiol 1962;47:305–13.
13. Keenaghan JB. The determination of lidocaine and prilocaine in whole blood by gas chromatography. Anesthesiology 1968;29:110–2.
14. Greenblatt DJ, Koch-Weser J. Drug therapy—clinical pharmacokinetics. N Engl J Med 1975;293:702–5.
15. Widdowson EM. Growth and composition of the fetus and newborn. In: Assali NS, ed. Biology of gestation. New York: Academic Press, Vol II 1968:1–44.
16. Tucker GT, Boyes RM, Bridenbaugh PO, Moore DC. Binding of anilide-type local anesthetics in human plasma. II. Implications in vivo, with special reference to transplacental distribution. Anesthesiology 1970;33:304–14.
17. Tucker GT, Wiklund L, Berlin-Wahlen A, Mather LE. Hepatic clearance of local anesthetics in man. J Pharmacokinet Biopharm 1977;5:111–22.

ANESTH ANALG
1982;61:109-14

Cardiovascular Effects of Morphine in Patients with Coronary Arterial Disease

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Large doses of morphine sulfate have been reported to cause myocardial lactate production and reduction in coronary blood flow in animals. Similar effects with clinical doses in man would significantly alter the management of cardiac patients. Eleven adult patients with significant coronary arterial disease and normal left ventricular ejection fraction were studied before and 30 minutes after infusion of morphine (0.25 mg/kg IV). Evaluation of myocardial metabolism showed an increase in coronary sinus oxygen content ($p < 0.001$) and a reduction in myocardial oxygen consumption. Myocardial lactate extraction was not altered. No change in coronary sinus blood flow was seen. It is concluded that infusion of morphine sulfate, 0.25 mg/kg IV, does not produce global myocardial ischemia in patients with coronary artery disease and normal ventricular function.

Key Words: HEART: blood flow, myocardial; ANALGESICS: morphine.

MORPHINE sulfate is commonly used as a preanesthetic agent in patients with heart disease (1) and has been popular as the primary anesthetic for coronary revascularization, particularly in patients with poor left ventricular function (2). The systemic hemodynamic effects of morphine have been described in detail in intact animals (3–5), in patients without heart disease (6), and in patients with valvular and coronary artery disease (7–10). In the varying doses (0.15 to 3.0 mg/kg) used in these studies, the drug exerts a minimal effect on systemic hemodynamics (2, 6–10).

Recently the effect of morphine on the coronary vascular bed has been examined. Vatner et al (3), studying conscious dogs with presumably normal coronary arteries, documented a decrease in coronary blood flow together with an increase in coronary vascular resistance at a constant heart rate, 15 minutes after a large dose of morphine (2 mg/kg of body weight). Left ventricular pressures and dimensions were not significantly altered, and myocardial contractility was slightly increased. The study by Schrank et al (5), in anesthetized dogs, also showed that morphine (2 to 10 mg/kg of body weight) decreased coronary blood flow and resulted in myocardial lactate production. Similar results in man at doses used clinically might detrimentally affect patients with coronary artery disease. Although the effect of morphine anesthesia on indirect indices of myocardial oxygenation has been described in patients undergoing coronary artery revascularization (11), evaluation of morphine on myocardial metabolism in patients with obstructive coronary arterial disease has not been reported. The goal of the present study was to examine the effects of morphine (0.25 mg/kg of body weight) on the coronary circulation of conscious patients with obstructive coronary artery disease by evaluation of myocardial metabolism.

Methods and Materials

After informed consent was obtained, 11 patients were studied according to a protocol approved by our

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Received from the Departments of Thoracic and Cardiovascular Surgery and Anesthesiology, Cedars-Sinai Medical Center, Los Angeles, California; and the Department of Anaesthesia, Dalhousie University, Halifax, Nova Scotia, Canada. Accepted for publication October 5, 1981.

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Human Subjects Committee. All patients had significant coronary arterial disease and were scheduled for elective coronary artery bypass grafting within 4 weeks of diagnostic cardiac catheterization. Friesinger score (12), an index of severity of coronary disease, had a mean value of 9.5. Mean left ventricular ejection fraction was 71%, indicating normal left ventricular function. Excluded from our study were patients with clinical diabetes mellitus, valvular heart disease, moderate arterial hypertension (diastolic blood pressure > 105 mm Hg), significant pulmonary disease, left ventricular end-diastolic pressure (LVEDP) > 20 mm Hg at rest or > 15 mm Hg after nitroglycerin, and patients with myocardial infarctions within 2 weeks. Patients with angiographically minimal ischemic mitral regurgitation were included. All patients had normal sinus rhythms.

The study was done in the operating room after instrumentation (to be described) and before induction of anesthesia. All patients were conscious and in the fasting state. Premedication, given to minimize anxiety, consisted of secobarbital, 100 mg given orally the night before surgery, and 3.0 mg/kg given orally 1 hour before going to the operating room. No attempt was made to modify preoperative medical regimens for the purpose of the study. Nine patients were receiving varying doses of propranolol (range: 40 to 240 mg/day; last dose 8 to 15 hours before the study). In addition, seven of these patients were taking isosorbide dinitrate, one patient was taking methyldopa, and one patient was taking prazosin.

In the operating room we introduced: (*a*) an 18-gauge cannula into the radial artery; (*b*) a thermodilution triple-lumen catheter (Edwards) by the Seldinger technique through the right internal jugular vein into the pulmonary artery; and (*c*) a coronary sinus catheter (Wilton-Webster Laboratories, Altadena, CA) by the same route and technique into the coronary sinus by fluoroscopy, so that the external thermistor was 10 to 20 mm inside the coronary sinus. The coronary sinus catheter measures total coronary sinus flow and is equipped with bipolar pacing electrodes.

To ensure that all patients had acceptable left ventricular filling pressures before the administration of morphine, intravenous normal saline or human albumin in normal saline solution (Albumisol) was administered in four patients in amounts adequate to achieve a pulmonary capillary wedge pressure of 12 mm Hg before control measurements were made (range of infusion: 200 to 850 ml). This goal was not achieved in two patients (patients 1 and 6, Table 2). Heart rate was held constant in all patients by atrial pacing at a subanginal rate calculated at 20% above the basal heart rate, but not exceeding 95 beats per minute. Morphine (0.25 mg/kg of body weight) was infused at the rate of 5 mg/min.

Control measurements with atrial pacing were performed at least 10 minutes after insertion of catheters to allow a stable resting state. Coronary blood flow was measured by the thermodilution technique described by Ganz et al (13). Arterial and coronary sinus blood samples were obtained simultaneously for determination of lactate and oxygen concentrations. Lactate levels were measured in duplicate by a modification of the Marbach method (14). Hemoglobin and oxygen saturation were measured by co-oximetry (Instrumentation Laboratory Co-oximeter, model 282). Systemic and pulmonary arterial, pulmonary capillary wedge, and right atrial pressures were measured on paper using a six-channel chart recorder (VR-6 Electronics for Medicine). Cardiac output was measured in duplicate. After completion of two sets of control measurements 5 minutes apart to ensure a stable base line, morphine was infused into an arm vein, with the patient unaware of it. Arterial blood pressure, ECG lead II, and the patient's clinical condition were continually monitored throughout. All patients were responsive and breathing oxygen by face mask during the study. Measurements were repeated 5, 15 (data not shown), and 30 minutes after infusion.

Hemodynamic indices were calculated from measured variables according to standard formulas (15). Metabolic indices were calculated as follows:

$$\text{lactate extraction ratio} = \frac{\text{ART (lactate)} - \text{CS (lactate)}}{\text{ART (lactate)}}$$

where ART (lactate) is the arterial lactate concentration (meq/L) and CS (lactate) is the coronary sinus lactate concentration (meq/L).

$$MV_{O_2} = CBF \times (ART\ [oxygen] - CS\ [oxygen])$$

where MV_{O_2} is oxygen consumption of the myocardium drained by the coronary sinus (predominantly the left ventricular myocardium) and CBF is coronary sinus blood flow.

Statistical analysis was done using the *t*-test for paired determinations, comparing measurements before and 30 minutes after infusion of morphine in each patient.

Results

The clinical characteristics of the patients are shown in Table 1. Hemodynamic data before and 30 minutes after completion of the morphine infusion for each patient are listed in Table 2. The mean dose of

morphine was 18.6 mg (range: 14.4 to 22.25 mg). In each patient, morphine produced a decrease in the calculated systemic vascular resistance (mean 18%, $p < 0.001$). This was accompanied by a 16% decrease in the mean arterial pressure for the entire group ($p < 0.001$). The mean pulmonary capillary wedge pressure did not change significantly, although it decreased in seven patients (8% to 60%), remained unchanged in three patients, and increased in one patient. In patients in whom preload, as reflected by the pulmonary capillary wedge pressure, was unchanged or elevated, the cardiac index increased (10% to 20%). The mean decrease of 15% in preload for the entire group was not significant, and no change occurred in mean cardiac index.

The myocardial metabolic findings for each patient are shown in Table 3. An increase in coronary sinus oxygen content was observed in 10 patients, with a 25% increase in mean coronary sinus oxygen content for the group ($p < 0.001$). In all except one patient, morphine produced a decrease in overall myocardial oxygen consumption (MV_{O_2}). In patient 1, an increase in myocardial oxygen consumption occurred with an accompanying increase in coronary blood flow. Myocardial lactate extraction was normal before infusion of morphine and increased by 25% afterwards, but

TABLE 1

Patients' Clinical Characteristics and Morphine Doses*

No. of patients (male/female)	11(9/2)
Age (yr)*	58 ± 9
Functional class (NYHA)†	
I/II	0/5
III/IV	4/2
Previous myocardial infarction	9
Coronary anatomy	
1-vessel disease	2
2-vessel disease	3
3-vessel disease	6
Coronary Friesinger score (12)*	9.5 ± 2.6
Ejection fraction*‡	0.71 ± 0.12
Dose of morphine (mg)	
Mean	18.6
Range	14.4–22.25

* Mean ± SD.

† NYHA, New York Heart Association.

‡ Measured by contrast ventriculography using right anterior oblique view.

TABLE 2

Hemodynamic Responses to Morphine in Patients with Coronary Artery Disease*

Patient no.	Intervention	HR	MAP	PCWP	SVR	CI
		beats/min	*mm Hg*		*dyne·sec·cm^{-5}*	*L/min/m^2*
1	Before	73	102	8	1807	2.10
	After	73	101	8	1566	2.38
2	Before	81	99	17	1013	3.84
	After	81	74	9	807	3.71
3	Before	73	98	13	1404	2.70
	After	73	82	12	1156	2.65
4	Before	83	112	12	1465	3.18
	After	83	91	8	1156	3.36
5	Before	70	95	15	1158	3.04
	After	70	80	23	795	3.34
6	Before	85	97	10	1074	3.15
	After	85	82	10	862	3.56
7	Before	74	90	13	1652	2.20
	After	74	91	10	1514	2.43
8	Before	78	93	15	1305	3.26
	After	78	69	6	1120	2.80
9	Before	70	127	13	2037	2.75
	After	70	109	8	1935	2.45
10	Before	78	96	13	1437	2.74
	After	78	75	13	848	3.30
11	Before	72	94	13	857	4.01
	After	72	75	12	707	3.79
Mean	Before	76 ± 5	100 ± 11	13 ± 2	1383 ± 354	3.00 ± 0.6
± SD	After	76 ± 5	84 ± 12	11 ± 5	1133 ± 392	3.07 ± 0.5
Significance		NS	$p < 0.001$	NS	$p < 0.001$	NS

* Abbreviations used are: HR, heart rate; MAP, systemic mean arterial pressure; PCWP, mean pulmonary capillary wedge pressure; SVR, systemic vascular resistance; CI, cardiac index.

TABLE 3

Myocardial Metabolic Responses to Morphine in Patients with Coronary Artery Disease*

Patient no.	Intervention	CBF	CVR	CS-O_2-content	MV_{O_2}	MLE	RPP
		ml/min	*mm Hg/ml/min*	*ml O_2/dl*	*ml/min*	%	
1	Before	118	0.81	4.8	20.4	−10	10,147
	After	171	0.55	7.1	24.5	29	9,782
2	Before	77	1.18	3.9	8.2	41	13,203
	After	81	0.86	3.9	7.9	38	9,396
3	Before	89	1.04	5.0	9.9	38	11,534
	After	91	0.82	6.7	8.4	27	9,271
4	Before	87	1.17	4.9	9.0	20	13,280
	After	87	0.98	5.2	8.4	19	12,264
5	Before	75	1.13	5.7	7.0	17	9,240
	After	98	0.65	8.6	5.4	14	9,100
6	Before	91	0.96	6.4	9.2	40	11,560
	After	104	0.76	7.6	8.8	43	10,030
7	Before	99	0.84	3.9	10.5	39	8,400
	After	82	1.02	5.9	8.0	61	9,490
8	Before	118	0.71	5.5	9.3	46	12,324
	After	121	0.51	6.8	8.1	39	9,438
9	Before	179	0.62	8.9	16.1	32	12,880
	After	136	0.77	9.3	13.1	45	10,780
10	Before	251	0.36	5.2	24.3	9	11,388
	After	170	0.38	6.5	14.4	27	9,164
11	Before	160	0.54	7.0	14.6	32	9,720
	After	154	0.43	9.4	10.0	42	8,064
Mean	Before	122 ± 54	0.85 ± 0.27	5.6 ± 1.4	12.6 ± 5.6	28 ± 17	11,243 ± 1,662
± SD	After	118 ± 35	0.70 ± 0.22	7.0 ± 1.7	10.6 ± 5.2	35 ± 13	9,706 ± 1,075
Significance		NS	$p < 0.05$	$p < 0.001$	NS	NS	$p < 0.05$

* Abbreviations used are: CBF, coronary blood flow; CVR, coronary vascular resistance; CS-O_2, oxygen content in coronary sinus blood; MV_{O_2}, myocardial oxygen consumption; MLE, myocardial lactate extraction; RPP, rate-pressure product.

this was not statistically significant. Mean coronary vascular resistance decreased by 18% ($p < 0.05$). No change in coronary blood flow was seen.

Arterial blood gas tensions were measured before and 30 minutes after morphine infusion in patients 4, 5, and 6. In patients 4 and 6, the results showed a decrease in P_{O_2} (120 → 110 torr, and 180 → 130 torr, respectively), and increase in P_{CO_2} (38 → 52 torr, and 46 → 51 torr, respectively), with a decrease in pH (7.40 → 7.29, and 7.39 → 7.31, respectively). Patient 5 showed more severe hypoventilation (P_{O_2}, 187 → 63 torr; P_{CO_2}, 44 → 67 torr; pH, 7.42 → 7.25).

No patient experienced chest discomfort, severe hypotension, or other adverse reactions during or after the morphine infusion. There were no alterations in cardiac rhythm in ST segment or T-wave patterns during the study.

Discussion

The clinical usefulness of morphine must be viewed in the context of both its hemodynamic effects and myocardial metabolic cost. This study examined the myocardial metabolic cost, specifically, change in myocardial oxygen supply and demand.

It is important to describe the patients studied accurately; the results obtained in one clinical or hemodynamic setting may not apply to all patients. All our patients had chronic stable angina or medically responsive unstable angina with significant coronary diseaase requiring myocardial revascularization. Six patients (55%) had angina, functional class III or IV. Although 82% of our patients gave a history of one or more previous documented myocardial infarctions, myocardial function, as evaluated by ejection fraction, was well preserved.

Morphine sulfate caused a significant reduction in peripheral resistance with a resulting significant decease in mean arterial pressure as cardiac output did not change. This alteration was present at 5 minutes after completion of the morphine infusion (unreported data) and persisted for at least 30 minutes. This effect may be dose related, as the study by Samuel et al (6) of patients without documented coronary artery disease showed a more transient response to lower doses of morphine (0.14 mg/kg of body weight). They found that the mean arterial pressure remained significantly reduced for up to 60

minutes (6). Severe hypotension, seen in patients with coronary artery disease receiving morphine at a faster infusion rate (8, 17), was not observed by us when the infusion rate was kept at 5 mg/min (18).

Cardiac index in our study reflects myocardial function responding to changes in preload, afterload, and contractility, as heart rate was constant. In each patient in whom the preload was unchanged or increased in the presence of a reduction in afterload, the cardiac index increased. The absence of a significant change in the cardiac index for our entire group is similar to the results reported in patients without cardiac disease (6), but contrasts with responses in patients with acute myocardial infarction in whom the drug causes a significant reduction (9). Although heart rate was held constant in our study, low doses of morphine in several studies in patients with spontaneous rhythm have shown no significant alterations in the rate (7, 9, 10, 19).

Relative to myocardial metabolism, morphine caused a decrease in myocardial oxygen needs, as shown by a significant increase in coronary sinus oxygen content without change in arterial content. This appears as a reduction in the calculated myocardial oxygen consumption, as global blood flow was unaltered. Another indicator of myocardial oxygenation is lactate. Normally, more than 20% of arterial lactate is extracted by the myocardium and used for adenosine triphosphate formation. Less than 10% extraction, or more lactate in coronary sinus than in arterial blood, indicates anaerobic metabolism and myocardial ischemia. In our patients, no significant alteration in myocardial lactate extraction was observed.

The etiology of the significant decrease in the calculated coronary vascular resistance that we observed is complex, reflecting, as it does, the opposing actions on the coronary vascular bed of coronary vasoconstriction, determined by a decrease in the myocardial oxygen demand (MV_{O_2}), and autoregulatory coronary vasodilation, caused by a decrease in the coronary perfusion pressure (mean arterial pressure) or coronary vasodilation as a direct result of morphine or indirectly due to diminished alpha-adrenergic tone.

The present study was performed under clinical conditions in patients with coronary artery disease who had received secobarbital before the administration of morphine. We cannot rule out the contribution of this medication to the hemodynamic and metabolic responses observed.

The limitations of the technique used for measuring coronary sinus blood flow in this study have been summarized elsewhere (13, 20, 21). We feel that this technique provides meaningful data regarding the magnitude and direction of changes in coronary blood flow when measured sequentially in the same patient. A potential technical criticism of the validity of coronary sinus blood flow determination by the thermodilution technique is present when right atrial pressure is elevated (22). In all of our patients, the positional stability of the catheter in the coronary sinus and the absence of major reflux into the mouth of the coronary sinus were assessed as suggested by Mathey et al (22).

We must be cautious in judging the myocardial safety of morphine in patients with coronary artery disease on the basis of our data. Alterations in regional myocardial blood flow and regional myocardial metabolism, particularly in areas of coronary obstruction, may not be reflected in the overall global evaluation of myocardial metabolic function. Our study could not examine regional myocardial pathophysiology, and the effect of morphine on these parameters remains to be determined. Furthermore, we studied only one dose of the drug, and responses to the doses of morphine used in the present study do not necessarily indicate responses that might be observed in patients during anesthesia and surgery using substantially greater doses of morphine.

In summary, we have documented the cardiovascular effects of morphine sulfate in patients with obstructive coronary artery disease with clinically relevant doses as used in coronary care units. The systemic hemodynamic effects observed are similar to those previously described in patients with coronary artery disease. As for global myocardial metabolism, we found an increase in coronary sinus oxygen content and no change in the normal pattern of myocardial lactate extraction. Whereas high doses of morphine in conscious animals may cause reduction in coronary blood flow and increases in myocardial contractility and myocardial lactate production, we saw none of these adverse effects in patients with coronary artery disease given 0.25 mg/kg of morphine intravenously.

ACKNOWLEDGMENTS

We would like to thank Drs. Aurelio Chaux, Alfonso Miyamoto, Hector Sustaita, Myles Lee, and Robert Kass for allowing us to include their patients in this study; Dr. Harvey Brown for performing the blood co-oximetry measurements; JoAnn Prause for statistical analysis; and Helen Schamroth and Kathleen Farrington for excellent secretarial assistance.

REFERENCES

1. Lyons SM, Clarke RSJ, Vulgaraki K. The premedication of

cardiac surgical patients—a clinical comparison of four regimes. Anaesthesia 1975;30:459–70.
2. Lowenstein E. Morphine anesthesia—a perspective. Anesthesiology 1971;35:563–5.
3. Vatner SF, Marsh JD, Swain JA. Effects of morphine on coronary and left ventricular dynamics in conscious dogs. J Clin Invest 1975;55:207–17.
4. Grover FL, Webb GE, Bevis V, Fewel JG. Effects of morphine and halothane anesthesia on coronary blood flow. Ann Thorac Surg 1976;22:429–35.
5. Schrank KP, Fewel JG, Arom KV, Trinkle JK, Webb GE, Grover FL. Effects of morphine anesthesia on myocardial contractility, blood flow and metabolism. J Surg Res 1980;28:319–27.
6. Samuel IO, Clarke RSJ, Dundee JW. Some circulatory and respiratory effects of morphine in patients without preexisting cardiac disease. Br J Anaesth 1977;49:927–33.
7. Grendahl H, Andersen A, Muller C. The effect of intravenous morphine in patients with mitral valvular disease and congestive heart failure. Acta Med Scand 1973;194:69–74.
8. Lowenstein E, Hallowell P, Levine FH, Daggett WM, Austen WG, Laver MB. Cardiovascular response to large doses of intravenous morphine in man. N Engl J Med 1969;281:1389–93.
9. Gould L, Reddy CVR, Oh KC, Kim SG, Becker WH. Hemodynamic effects of morphine in cardiac disease. J Clin Pharmacol 1978;18:448–56.
10. Leaman DM, Nellis SH, Zelis R, Field JM. Effects of morphine sulfate on human coronary blood flow. Am J Cardiol 1978;41:324–6.
11. Kistner JR, Miller ED, Lake CL, Ross WT. Indices of myocardial oxygenation during coronary-artery revascularization in man with morphine versus halothane anesthesia. Anesthesiology 1979;50:324–30.
12. Friesinger GC, Page EE, Ross RS. Prognostic significance of coronary arteriography. Trans Assoc Am Physicians 1970;83:78–92.
13. Ganz W, Tamura K, Marcus HS, Donoso R, Yoshida S, Swan HJC. Measurement of coronary sinus blood flow by continuous thermodilution in man. Circulation 1971;44:181–95.
14. Marbach EP, Weil MH. Rapid enzymatic measurements of blood lactate and pyruvate. Clin Chem 1967;13:314–25.
15. Yang SS, Bentivoglio LG, Maranhao V, Goldberg H. From cardiac catheterization data to hemodynamic parameters. Philadelphia: FA Davis, 1972:37–43.
16. Deleted in proof.
17. Stoelting RK, Gibbs PS. Hemodynamic effects of morphine and morphine nitrous oxide in valvular heart disease and coronary artery disease. Anesthesiology 1973;38:45–52.
18. Lappas DG, Geha D, Fischer JE, Laver MB, Lowenstein E. Filling pressures of the heart and pulmonary circulation of the patient with coronary artery disease after large intravenous doses of morphine. Anesthesiology 1975;42:153–9.
19. Papper EM, Bradley SE. Hemodynamic effects of intravenous morphine and pentothal sodium. J Pharmacol Exp Ther 1942;74:319–23.
20. Weisse AB, Regan TJ. A comparison of thermodilution coronary sinus blood flows and krypton myocardial blood flows in the intact dog. Cardiovasc Res 1974;8:526–33.
21. Simonsen S. Aspects of cardiac venous flow measured by the continuous infusion thermodilution technique. Cardiology 1977;62:51–62.
22. Mathey DG, Chatterjee K, Tyberg JV, Lekven J, Brundage B, Parmley WW. Coronary sinus reflux: a source of error in the measurement of thermodilution coronary sinus flow. Circulation 1978;57:778–86.

ANESTH ANALG
1982;61:115-9

Cardiovascular Effects of Sufentanil Anesthesia

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SEBEL, P. S., AND BOVILL, J. G.: Cardiovascular effects of sufentanil anesthesia. Anesth Analg 1982;61:115-9.

Sufentanil is a new synthetic opiate analgesic that is 4520 times more potent than morphine in animal experiments. This study evaluated the cardiovascular effects of sufentanil, 15 μg/kg, and air/O_2 used as a complete anesthetic with 50% inspired oxygen (air/O_2 mixture) in 40 adult patients undergoing elective or emergency cardiac surgery. Statistically significant changes included a decrease in systolic pressure 5 minutes after induction, decreases in systolic and mean blood pressures and peripheral resistance before incision, and a decrease in systolic pressure below control levels 2 minutes after incision. The diastolic pressure increased significantly 5 minutes after sternotomy. Two patients became hypotensive on induction of anesthesia and 16 patients developed hypertension related to sternotomy. These results indicate that sufentanil anesthesia provides good cardiovascular stability for cardiac surgery and is a technique worthy of further evaluation.

Key Words: ANESTHETICS, Intravenous: sufentanil; ANALGESICS: sufentanil; ANESTHESIA: cardiovascular.

SUFENTANIL, *N*-{4-(methoxymethyl)-1-[2-(2-thienyl)ethyl]-4-piperidinyl}-*N*-phenylpropanamide, is a new synthetic opiate analgesic. A *N*-4 substituted derivative of fentanyl (Figure), its chemistry was described in 1976 by Van Bever et al (1). Studies using the tail withdrawal reflex in rats indicate that sufentanil is 4520 times more potent than morphine (2) but with a high therapeutic ratio, the LD_{50}/ED_{50} ratio being 25,211 whereas morphine and fentanyl have LD_{50}/ED_{50} ratios of 69 and 277, respectively (2).

Clinical experience in man suggests that sufentanil is 5 to 10 times more potent than fentanyl and that doses up to 10 μg/kg produce little change in cardiovascular function (3-5). Infusion of sufentanil, 40 μg/kg/min, produces little change in cardiovascular dynamics in atropinized dogs and its use as a complete opiate anesthetic in man has been suggested (6). In this study, we have investigated the cardiovascular effects of sufentanil, 15 μg/kg, as an anesthetic for cardiac surgery in man.

Methods

The study included 40 adults undergoing elective or emergency cardiac surgery. All consented to the investigation. Patient data are shown in Table 1.

Patients undergoing coronary artery surgery were taking beta-blocking drugs, which were discontinued the evening before surgery. Twenty-seven of the patients had flow-directed pulmonary arterial catheters (Swan-Ganz) inserted via the subclavian vein under fluoroscopic control the day before surgery. All patients were premedicated with lorazepam, 4 to 5 mg, orally 1.5 hours before surgery. On arrival in the operating room, ECG leads were applied and two large-gauge peripheral venous cannulas, a #18 French gauge radial arterial cannula, and a central venous catheter (if no Swan-Ganz catheter) were inserted percutaneously under local anesthesia. After preoxygenation, pancuronium, 2 mg, was given intravenously followed by sufentanil, 15 μg/kg, injected over a 2-minute period. During the injection of sufentanil, an additional 6 mg of pancuronium was given in divided doses. When the patient stopped breathing, respiration was continued manually. Five minutes after the start of induction, the patient's trachea was intubated, a nasogastric tube was passed, and esophageal, nasopharyngeal, and muscle thermocouples were positioned. The bladder was catheterized. Ventilation was continued with air/O_2 with F_{IO_2} = 0.5. Ventilation was adjusted to maintain an end-tidal CO_2 concentration of 4.5% to 5%. Persistent hypertension

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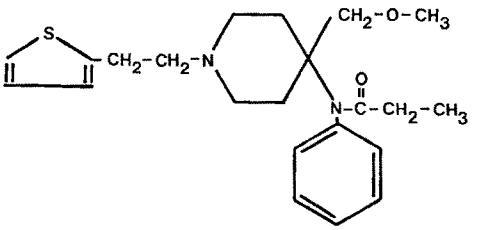


FIGURE. Molecular structure of sufentanil.

TABLE 1
Patient Data

No. of patients (male/female)	40 (30/10)
Weight (kg)*	71.2 ± 1.48
Age (yr)*	58.3 ± 1.44
Type of surgery	
Coronary artery	31
Aortic valve	3
Mitral and aortic valve	3
Atrial septal defect	1
Aneurysm and coronary artery	1
Mitral and aortic valve and coronary artery	1

* Value is mean ± SEM.

(an increase in systolic pressure more than 20 mm Hg above control levels) was treated with sufentanil, 250 to 500 μg, given intravenously. If this did not correct the hypertension, sodium nitroprusside, 10 to 100 μg/min, was given by intravenous infusion.

During anesthesia and surgery, ECG, heart rate, systolic and diastolic blood pressures, and central venous pressure were continuously monitored. The output from the arterial pressure module (Hewlett-Packard) was connected to a Philips cardiac output computer. The computer calculates the stroke volume on a beat-to-beat basis using the characteristic impedance pulse contour method (7).

Calibration factors are included in the computer program to correct for changes in mean arterial pressure and heart rate as well as for changes in aortic impedance with age. This method of pulse contour analysis correlates well with conventional methods of cardiac output determination even during marked changes in blood pressure, heart rate, and/or systemic vascular resistance or during arrhythmias (8, 9). Although designed for use with a pressure wave form derived from the central aorta, it has been shown that the results are also reliable with brachial or radial artery pressure as used in this study (Smith NT, Wesseling KH, Weber JAP, De Wit B. Preliminary evaluation of a pulse contour cardiac output computer in man: feasibility of brachial or radial artery pressures. Proceedings of the San Diego Biomedical Symposium 1974;13:113–9).

To obtain absolute values for cardiac output using pulse contour analysis, it is necessary to precalibrate the machine using another method of cardiac output determination (e.g., thermodilution) as a standard. This was not done in this study; therefore, control values of cardiac index reported are not absolute values although all changes relative to control values are accurate.

Systolic, diastolic, and right atrial pressures, heart rate, and cardiac output were recorded every minute, and pulmonary arterial and pulmonary capillary wedge pressure (when available) were measured every 2 to 5 minutes. Derived cardiovascular parameters were calculated using standard formulas. Fluid administered in the period before cardiopulmonary bypass was restricted to 300 to 500 ml of 5% glucose.

Data are presented as mean values ± SEM. Analysis of variance was used to determine significance of changes within groups. A modified *t*-test was used to identify significant differences from control values using critical values for p calculated according to the method of Bonnferroni (10).

Results

As it is impossible to present numerical cardiovascular data for each minute of anesthesia and surgery, data related to points of maximum stimulation are shown in Table 2.

Systolic blood pressure decreased 5 minutes after induction, but there were no other statistically significant cardiovascular changes related to induction or intubation. Immediately before incision, when patients had been without stimulation for approximately 20 minutes, there were statistically significant decreases in systolic and mean pressures and in the rate-pressure products. The reduction in systolic pressure was still present 2 minutes after skin incision. There was a statistically significant increase in diastolic pressure 5 minutes after sternotomy. No arrhythmias that could be related to the administration of sufentanil were seen. Data more than 10 minutes after sternotomy are not reported owing to wide variations caused by surgical manipulation of the heart.

The mean data for all patients shown in Table 2 obscure marked changes in cardiovascular dynamics occurring in individual patients. For this reason we also reviewed cardiovascular data from individual patients. Two patients had marked decreases in blood pressure on induction of anesthesia, from 116 to 60 mm Hg systolic in one patient and from 150 to 70 mm Hg in the other. These decreases in pressure responded to the administration of metaraminol, 1

TABLE 2

Cardiovascular Parameters for 40 Patients Receiving Sufentanil, 15 μg/kg, and Air/O_2*

	Control	Induction		Intubation		Before incision	Incision		Sternotomy		
		+2 min	+5 min	+ 2 min	+5 min		+2 min	+5 min	+2 min	+5 min	+10 min
Systolic pressure (mm Hg)	147.5 ±3.04	137.1 ±3.68	129.9 ±3.78‡	138.1 ±4.14	134.6 ±4.27	125.1 ±2.69‡	132.0 ±4.66†	140.9 ±3.12	150.9 ±3.12	154.5 ±3.28	153.2 ±4.01
Diastolic pressure (mm Hg)	74.0 ±1.34	71.0 ±1.87	68.9 ±2.26	72.6 ±2.29	70.3 ±2.24	68.8 ±1.75	73.7 ±2.06	76.3 ±2.05	81.7 ±2.17	82.3 ±2.17†	79.7 ±2.18
Mean pressure (mm Hg)	9.5 ±1.58	93.0 ±2.19	89.2 ±2.61	94.4 ±2.71	91.7 ±2.76	87.6 ±1.89†	93.1 ±2.58	97.8 ±2.58	104.8 ±2.26	106.4 ±2.33	104.2 ±2.49
Central venous pressure (mm Hg)	0.9 ±0.59	2.2 ±0.61	1.9 ±0.59	1.8 ±0.58	1.0 ±0.53	1.2 ±0.51	1.9 ±0.41	1.6 ±0.44	1.2 ±0.39	0.8 ±0.40	1.2 ±0.42
Heart rate (beats/min)	72.8 ±1.92	73.9 ±2.01	75.8 ±2.34	77.6 ±2.85	75.6 ±2.19	69.3 ±2.09	69.3 ±1.98	70.8 ±2.11	75.2 ±2.39	75.7 ±2.29	77.2 ±3.22
Pulmonary arterial pressure (mm Hg)	15.1 ±1.62	14.9 ±1.70	14.4 ±1.73	15.8 ±2.30	14.4 ±2.16	12.5 ±1.47	13.8 ±1.66	14.7 ±2.05	12.9 ±1.91	14.5 ±1.60	13.4 ±1.67
Pulmonary capillary wedge pressure (mm Hg)	7.3 ±1.15	6.9 ±0.87	6.1 ±0.84	6.2 ±1.08	6.0 ±0.99	6.1 ±1.00	6.9 ±1.28	7.1 ±1.43	6.4 ±1.70	6.9 ±1.41	4.7 ±0.94
Cardiac index (L/min/m^2)	3.4 ±0.17	3.3 ±0.18	3.3 ±0.19	3.4 ±0.18	3.4 ±0.16	3.0 ±0.14	3.0 ±0.16	3.1 ±0.16	3.2 ±0.16	3.3 ±0.16	3.4 ±0.17
Stroke index (ml/beat/m^2)	47.1 ±2.12	44.2 ±1.73	43.8 ±1.88	44.8 ±1.92	45.1 ±1.71	44.3 ±1.97	43.5 ±2.07	43.8 ±1.97	43.4 ±1.76	43.2 ±1.84	44.0 ±1.96
Rate-pressure product	10,793 ±402.1	10,227 ±460.10	9,972 ±498.4	10,806 ±557.4	10,293 ±508.7	8,739 ±380.6†	9,307 ±487.6	10,060 ±424.3	11,473 ±519.2	11,741 ±456.3	11,886 ±608.7
Peripheral resistance (dyne·sec/cm^5)	1,345 ±66.4	1,309 ±69.1	1,228 ±58.1	1,266 ±57.9	1,234 ±48.3	1,325 ±56.4	1,456 ±74.5	1,482 ±74.2	1,511 ±74.9	1,539 ±73.6	1,441 ±61.8
Left ventricular stroke work index (gm·m/m^2/beat)	58.2 ±3.88	49.8 ±2.83	48.1 ±3.14	52.8 ±3.09	48.7 ±3.02	47.6 ±2.87	50.0 ±3.72	51.0 ±3.41	55.5 ±4.33	57.0 ±4.35	63.2 ±4.84
Pulmonary vascular resistance (dyne·sec/cm^5)	138.2 ±16.2	117.9 ±18.28	120.0 ±20.42	133.5 ±14.15	122.3 ±14.95	103.8 ±10.63	108.8 ±12.83	117.5 ±18.20	88.8 ±10.55	100.3 ±10.36	105.2 ±14.64

* Values are means ± SEM.
† $p < 0.05$.
‡ $p < 0.01$.

mg, given intravenously. They occurred in patients with coronary artery disease (but, unfortunately, without Swan-Ganz catheters). The decreases in blood pressure were accompanied by modest reductions in central venous pressure. In addition, one patient developed a sudden increase in heart rate from 67 to 76 beats per minute in response to the stimulus of intubation. Sixteen patients developed hypertension (an increase of more than 20 mm Hg above preanesthetic levels) following sternotomy. In 12 of these 16 patients sufentanil, 250 to 500 μg, controlled the hypertension; in four patients sodium nitroprusside infusion was necessary. After cardiopulmonary bypass, six patients required dopamine for inotropic support and one patient continued to require sodium nitroprusside. Five patients received sufentanil, 250 μg, during closure of the chest because of signs of light anesthesia. The mean total dose of sufentanil given over the whole operation was 19.4 μg/kg (range 15 to 23.4 μg/kg). The duration of surgery was from 3 to 6 hours. No other anesthetic adjuncts were used. All patients were routinely ventilated until the morning after surgery. One patient did not survive cardiopulmonary bypass. Following direct questioning 4 to 5 days after surgery, none of the remaining 39 patients reported any intraoperative awareness.

Discussion

The use of large doses of opiate analgesics as complete anesthetic agents was stimulated by the observation of Lowenstein et al (11), that morphine, 1 mg/kg, produced minimal alterations in circulatory

dynamics in patients with aortic valve disease. Morphine, 1 to 3 mg/kg, as a complete anesthetic is not free of complications. These include hypotension (12, 13), hypertension (14), cardiovascular depression when combined with nitrous oxide (15), increased circulating levels of catecholamines (16, 17), increased blood and fluid requirements (18), and the inability of even very high doses of morphine to abolish awareness reliably, especially in fit patients (12).

Anesthesia with fentanyl, 50 to 110 μg/kg, was proposed by Stanley and colleagues (19, 20) as an improvement on morphine anesthesia, producing greater cardiovascular stability than morphine. Fentanyl also suppresses hormonal responses to surgery, although not to cardiopulmonary bypass (21, 22). Whether this reduction in stress response is of clinical benefit remains unclear at this time. Fentanyl does not always provide total absence of recall and one case of awareness after fentanyl anesthesia has been reported (23), but there is as yet insufficient evidence to judge whether the incidence of awareness is lesser or greater than with morphine anesthesia.

It has been suggested that the more potent an opiate analgesic, the less the incidence of side effects and the greater the cardiovascular stability obtained (24). If this were true, then sufentanil would be preferable to fentanyl as an opiate anesthetic. However, during a double-blind comparison of sufentanil, 2 μg/kg, and fentanyl, 20 μg/kg, used as anesthetic supplements, no significant differences were found (4), nor were any differences found between the effects of fentanyl, 7 μg/kg, and sufentanil, 0.7 μg/kg, on systemic or coronary hemodynamics in healthy patients (25).

In the present study, an evaluation was made of the cardiovascular effects of sufentanil given in an "open" manner. Cardiovascular stability was obtained in most cases. In the two patients who became hypotensive on induction, the hypotension was accompanied by modest decreases in central venous pressure, and we may speculate that in these two patients cardiac filling may have decreased below the critical level necessary to maintain adequate output.

Sufentanil, 15 μg/kg, is not capable of totally preventing the hypertensive response related to sternotomy (26). The reason why patients become hypertensive following sternotomy is unclear. The hypertension is not related to other signs of light anesthesia, e.g., tachycardia, lacrimation, or perspiring. Clinical observation suggests that the hypertension is not directly related to sternotomy but rather to pericardial and myocardial manipulation. It is possible that a specific cardiogenic reflex is involved (27). Hypertension in the present study was in most cases satisfactorally controlled with sufentanil supplementation, but 10% of the patients also required vasodilator therapy. We suggest that in future studies sufentanil supplementation be routinely given before sternotomy.

Most reports on the use of high-dose fentanyl anesthesia involve a slow administration of the drug (300 μg/min) with frequent supplementation (19–21) which gives cardiovascular stability. It has been our practice to administer a large dose of fentanyl (60 μg/kg) over a 2-minute period (22, 28, 29) for anesthetic induction. This provides cardiovascular stability similar to that observed in patients receiving a slow infusion of fentanyl (29). For this reason we administered sufentanil as a single bolus injection in this study. The cardiovascular results obtained are at least as satisfactory as those reported with fentanyl. The dose of sufentanil used in this study has been found to give satisfactory depression of the electroencephalogram (30) and was therefore chosen for use in the present study.

The only sign of inadequate anesthesia seen before bypass in our patients was a 10 beats per minute increase in heart rate in response to intubation in one patient. None of the other patients had increases in heart rate in response to any stimuli. After direct questioning, no patients reported any intraoperative awareness, although episodes of awareness reported during opiate anesthesia are sporadic and this series may have been too small to detect a possibly rare event.

This study demonstrates that sufentanil, 15 μg/kg, provides stable, pollution-free anesthesia for cardiac surgery. A double-blind comparison with fentanyl in a large series would be necessary to establish its position fully.

REFERENCES

1. Van Bever WFM, Niemegeers CJE, Schellekens KHL, Janssen PAJ. N-4-substituted 1-(2-arylethyl)-4-piperidinyl-N-phenylpropanamides, a novel series of extremely potent analgesics with unusually high safety margins. Arzneim Forsch 1976;26:1548–51.
2. Niemegeers CJE, Schellekens KHL, Van Bever WFM, Janssen PAJ. Sufentanil, a very potent and extremely safe morphine-like compound in mice, rats and dogs. Arzneim Forsch 1976;26:1551–6.
3. De Castro J. Practical applications and limitations of analgesic anesthesia: a review. Acta Anaesthesiol Belg 1976;27:107–28.
4. Rolly G, Kay B, Cockx F. A double blind comparison of high doses fentanyl and sufentanil in men: influence on cardiovascular, respiratory and metabolic parameters. Acta Anaesthesiol Belg 1979;30:247–54.

5. Van de Walle J, Lauwers P, Adriaensen H. Double blind comparison of fentanyl and sufentanil in anesthesia. Acta Anaesthesiol Belg 1976;27:129–38.
6. Reddy P, Liu W, Port D, Gillmor S, Stanley TH. Comparison of haemodynamic effects of anaesthetic doses of alphaprodine and sufentanil in the dog. Can Anaesth Soc J 1980;27:345–50.
7. Wesseling KH, Smith NT, Nichols WW, Weber H, De Wit B, Beneken JEW. Beat to beat cardiac output from the arterial pressure contour. In: Feldman SA, Leigh JM, Spierdijk J, eds. Measurement in anaesthesia. Leiden: Leiden University Press, 1974:150–64.
8. Wesseling KH, Purschke R, Smith NT, Wust HJ, De Wit B, Weber HAP. A computer module for the continuous monitoring of cardiac output in the operating theatre and ICU. Acta Anaesthesiol Belg 1976;27:327-41.
9. Thomas B. Monitoring of cardiac output by pulse contour method. Acta Anaesthesiol Belg 1978;29:259–70.
10. Wallenstein S, Zucker CL, Fleiss JL. Same statistical methods useful in circulation research. Circ Res 1980;47:1–9.
11. Lowenstein E, Hallowell P, Levine FH, Daggett WM, Austen WG, Laver MG. Cardiovascular responses to large doses of intravenous morphine in man. N Engl J Med 1969;281:1389–93.
12. Lowenstein E. Morphine anesthesia: a perspective. Anesthesiology 1971;35:563–5.
13. Arens JF, Benbow BP, Oschner JL, Theard R. Morphine anesthesia for aortocoronary bypass procedures. Anesth Analg 1972;51:901–9.
14. Kistner JR, Miller ED, Lake CL, Ross WT. Indices of myocardial oxygenation during coronary-artery revascularization in man with morphine versus halothane anesthesia. Anesthesiology 1979;50:324–30.
15. McDermott RW, Stanely TH. The cardiovascular effects of low concentrations of nitrous oxide during morphine anesthesia. Anesthesiology 1974;41:89–91.
16. Hasbrouk JD. Morphine anesthesia for open-heart surgery. Ann Thorac Surg 1970;10:364–9.
17. Vasko JS, Henney P, Brawley RK, Oldham HN, Morrow AG. Effects of morphine on ventricular function and myocardial contractile force. Am J Physiol 1966;210:329–34.
18. Stanley TH, Gray NH, Stanford W, Armstrong R. The effects of high-dose morphine on fluid and blood requirements in open-heart operations. Anesthesiology 1973;38:536–41.
19. Stanley TH, Webster LR. Anesthetic requirements and cardiovascular effects of fentanyl-oxygen and fentanyl-diazepam-oxygen anesthesia in man. Anesth Analg 1978;57:411–26.
20. Lunn JK, Stanley TH, Eisele J, Webster L, Woodward A. High dose fentanyl anesthesia for coronary artery surgery: plasma fentanyl concentrations and influence of nitrous oxide on cardiovascular responses. Anesth Analg 1979;58:390–5.
21. Stanley TH, Berman L, Green O, Robertson D. Plasma catecholamine and cortisol responses to fentanyl-oxygen anesthesia for coronary-artery operations. Anesthesiology 1980;53:250–3.
22. Sebel PS, Bovill JG, Schellekens APM, Hawker CD. Hormonal responses to high dose fentanyl anaesthesia. Br J Anaesth 1981;53:941–8.
23. Mummaneni N, Rao TLK, Montoya A. Awareness and recall with high-dose fentanyl-oxygen anesthesia. Anesth Analg 1980;59:948–9.
24. De Castro J, Van de Water A, Wouters L, Xhonneux R, Reneman R, Kay B. Comparative study of cardiovascular, neurological and metabolic side-effects of eight narcotics in dogs. Acta Anaesthesiol Belg 1979;30:5–99.
25. Larsen R, Sonntag H, Schenk HD, Radke J, Hilfiker O. Die Wirkungen von Sufentanil und Fentanyl auf hämodynamik Coronardurchblutung und myocardialen Metabolismus des Menschen. Anaesthetist 1980;29:277–9.
26. Chambers DA. Anesthesia for the patient with acquired valvular heart disease. In: Kaplan JA, ed. Cardiac anesthesia. New York: Grune & Stratton, 1979:220.
27. James TN, Isobe JH, Urthaler F. Analysis of components in a cardiogenic hypertensive chemoreflex. Circulation 1975;52: 179–92.
28. Bovill JG, Sebel PS. Pharmacokinetics of high-dose fentanyl: a study in patients undergoing cardiac surgery. Br J Anaesth 1980;52:795–802.
29. Sebel PS, Bovill JG, Wauquier A, Rog P. Effects of high-dose fentanyl anesthesia on the electroencephalogram. Anesthesiology 1981;55:203–11.
30. Bovill JG, Sebel PS, Wauquier A, Rog P. Effects of sufentanil anaesthesia on the electroencephalogram in man. Br J Anaesth (in press 1982).

ANESTH ANALG
1982;61:120-6

Prevention of Nitroprusside Toxicity with Thiosulfate in Dogs

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IVANKOVICH, A. D., BRAVERMAN, B., SHULMAN, M., AND KLOWDEN, A. J.: Prevention of nitroprusside toxicity with thiosulfate in dogs. Anesth Analg 1982;61:120-6.

The dose of sodium nitroprusside (SNP) that can be safely used for deliberate hypotension is limited by the toxicity of cyanide (CN), its metabolite. The cardiovascular effect of combining sodium thiosulfate with SNP in dogs was investigated to determine whether this combination might protect against CN toxicity without altering the SNP-induced hemodynamic changes. Ten pentobarbital-anesthetized dogs were divided into two equal groups, intubated, and maintained on room air. Control animals (group C) received an infusion of 0.7 ml/min of normal saline; test dogs (group T) received a bolus of sodium thiosulfate, 30 mg/kg, followed by 30 mg/kg/hr infused at 0.7 ml/min. Hypotension (mean blood pressure of 60 mm Hg) was then induced and maintained by SNP for 5 hours in both groups. In group T, heart rate (HR) first increased, then returned to base levels after 60 minutes of hypotension, whereas in group C, HR decreased steadily and after 5 hours was 29 beats per minute less than its initial rate. Cardiac output increased initially in both groups and then returned to starting levels after 180 minutes of hypotension. The SNP infusion rate, mean dose 0.8 mg/min (37 ± 5 μg/kg/min) initially in both groups, was kept at this rate throughout hypotension for group T, but had to be reduced steadily to 0.17 mg/min (8 ± 1 μg/kg/min) for group C. The whole-blood CN level in group T rose to 39 ± 9 μg/dl; in group C, it rose to 381 ± 44 μg/dl at 150 minutes, then decreased to 304 ± 114 μg/dl when the SNP infusion rate was at its minimum. Endogenous plasma thiosulfate concentration was initially 1.3 ± 0.32 mg/dl in group C and 1.04 ± 0.09 mg/dl in group T. During SNP infusion, plasma levels of endogenous thiosulfate decreased to 0.91 ± 0.16 mg/dl ($p < 0.05$) in group C, whereas in group T the infusion of thiosulfate increased the plasma levels of thiosulfate and maintained them at approximately 15.5 mg/dl for 300 minutes. Blood gas tensions and pH were not significantly different between the two groups during most of the study; the venous pH decreased in both groups but to a greater extent in group C. These findings suggest that thiosulfate is effective in maintaining a safe blood CN concentration when high doses of SNP are required to maintain hypotension for 5 hours without altering the SNP-induced hemodynamic effects.

Key Words: ANESTHETIC TECHNIQUES: hypotensive; TOXICITY: cyanide.

THE PHARMACOLOGIC properties and therapeutic uses of sodium nitroprusside (sodium nitrosylpentacyanoferrate (III); SNP) have been extensively reviewed (1, 2). Its potent, yet readily reversible, hypotensive effects have attracted considerable interest for intraoperative and clinical applications, but its potential for cyanide (CN) toxicity has limited dosages and duration of administration. From a variety of CN antidotes, two, thiosulfate and hydroxocobalamin, have been recommended (3, 4) as possible adjuvants for the prevention of SNP toxicity. The purpose of the present study was to determine whether thiosulfate, administered during SNP-induced hypotension, (*a*) protects against CN toxicity, (*b*) produces deleterious side effects, and (*c*) interferes with the hemodynamic effects of SNP. The value of the canine model was established in earlier experiments (3, 5, 6).

Methods

Ten mongrel dogs of either sex, 11 to 30 kg each, were anesthetized with pentobarbital, 30 mg/kg IV, and endotracheally intubated following administration of pancuronium, 0.2 mg/kg IM. Ventilation was controlled by a Harvard ventilator pump (15 ml/kg at

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Received from the Departments of Anesthesiology, Abraham Lincolon School of Medicine, University of Illinois, and the Illinois Masonic Medical Center, Chicago. Accepted for publication October 2, 1981.

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14 breaths/min) using room air and adjusted to maintain $Paco_2$ at approximately 35 mm Hg before the start of the experiment. Respiratory rate and tidal volume were kept constant for the duration of the experiment. Supplemental doses of pentobarbital, 50 mg IV, were given every 60 minutes. No supplemental pancuronium was given. A femoral arterial catheter was advanced to the abdominal aorta for pressure recordings and blood sampling. A femoral venous catheter was used for SNP infusions, and a peripheral vein was cannulated for either saline or sodium thiosulfate infusions. A Swan-Ganz catheter was positioned in the pulmonary artery for measurement of cardiac output (thermal dilution), pulmonary arterial pressure, pulmonary capillary wedge pressure (PCWP), right atrial pressure, and mixed venous blood gas tensions; the urinary bladder was catheterized. All dogs received a total of 250 ml of Ringer's solution and 60 ml of 10% Gentran 40 (Travenol) IV, before the start of the experiment.

Animals were randomly divided into two groups of five each; control dogs (group C) received an infusion of normal saline, 0.7 ml/min, whereas test animals (group T) received a bolus injection of sodium thiosulfate, 30 mg/kg, followed by an infusion of thiosulfate, 30 mg/kg/hr, delivered in a volume of 0.7 ml/min. After 10 minutes, an infusion of SNP (50 mg/500 ml 5% dextrose/water; protected from light) was begun, and mean arterial blood pressure (MAP) was decreased to 60 mm Hg; the infusion rate was periodically readjusted to maintain this level of hypotension for 5 hours. Blood samples were taken before and after the thiosulfate infusion and every 30 minutes during SNP infusion. Sample volumes were replaced with Ringer's solution, and bicarbonate was given sparingly to correct severe acidosis without fluid overload. The experiment was terminated after 5 hours. A segment of gracilus muscle was removed and frozen for tissue CN analysis.

Pressures were measured with Statham P23Dc pressure transducers and recorded on an Electronics for Medicine VR-12 oscillographic recorder. Recordings were also made of the electrocardiogram (ECG) (lead II) and the thermal dilution curves of cardiac output. Cyanide levels were determined by the microdiffusion method (7) in a commercial laboratory (Bio-Science Laboratories, Inc, Van Nuys, CA). Thiocyanate and thiosulfate were determined spectrophotometrically (8). Blood gas tensions and pH were determined on an IL blood gas analyzer model 113. Data were compared by two-way analysis of variance for repeated measurements in the same subject for overall significance (9). Comparisons between groups were made by the Student-Newman-Keuls method, and statistical significance was accepted at the 0.05 level of probability.

Results

The bolus injection and infusion of thiosulfate did not result in any noticeable changes in cardiovascular measurements, blood-gas tensions, or pH values. At the initiation of the SNP infusion at 0.8 mg/min (37 ± 5 μg/kg/min) in both groups, MAP steadily decreased until it reached 60 mm Hg. In each dog, this level of hypotension was established and then was maintained over a 5-hour period (Fig 1). Heart rate (HR) increased after 30 minutes of SNP in group T (Fig 1) whereas in group C, HR significantly decreased. It returned to initial levels in thiosulfate-treated dogs by 90 minutes and remained at this rate for the remainder of the SNP infusion; however, HR continued to decrease in group C and was consistently lower than in group T during the entire SNP infusion.

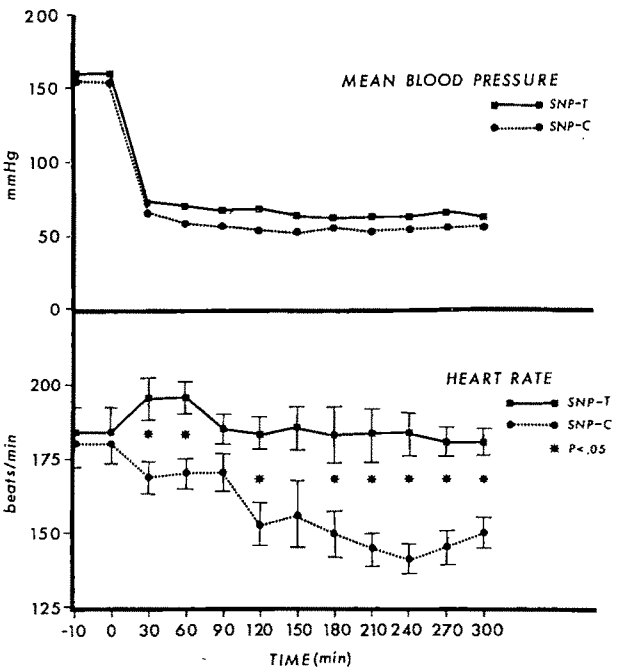


FIG 1. Mean blood pressure and heart rate in two groups of dogs given sodium nitroprusside (SNP) intravenously from time 0 to 300 minutes, maintaining hypotension at 60 mm Hg. Solid symbols and solid lines represent test group (SNP-T) given thiosulfate, 30 mg/kg, bolus at −10 minutes followed by 30 mg/kg/hr infusion until the end of the experiment. Solid symbols and dotted lines represent control animals (SNP-C) given saline without thiosulfate. SNP infusion was given from time 0 to 300 minutes; N = 5 in each group; * denotes significant differences between groups ($p < 0.05$). Vertical lines are standard error (too small to display on mean arterial pressure (MAP) scale).

TABLE 1

Effects of Sodium Nitroprusside (SNP) on Group C (Saline) and Group T (Thiosulfate) Dogs*

Time	Q_t		$\overline{PCWP}$		$\overline{PAP}$		$\overline{RAP}$		Thiosulfate	
	C	T	C	T	C	T	C	T	C	T
min	*L/min/kg*				*mm Hg*				*mg/dl*	
0	0.28 ± 0.03	0.26 ± 0.04	8.6 ± 0.5	6.8 ± 0.5	19 ± 2	18 ± 2	4.6 ± 1.0	6.6 ± 1.1	1.30 ± 0.32	1.04 ± 0.09
30	0.38 ± 0.04†	0.29 ± 0.05†	10.0 ± 1.6	6.8 ± 0.5	19 ± 2	16 ± 1	6.4 ± 1.0	6.2 ± 1.0	1.10 ± 0.32†	15.5 ± 1.1†
60	0.38 ± 0.02†	0.31 ± 0.05†	10.2 ± 1.4	6.6 ± 0.9	12 ± 2	16 ± 1	6.6 ± 0.7	5.6 ± 0.7	1.04 ± 0.19†	15.6 ± 1.1†
90	0.40 ± 0.03†	0.33 ± 0.06†	10.2 ± 1.4	6.2 ± 1.0	22 ± 2	17 ± 1	6.0 ± 0.5	6.8 ± 0.5	0.91 ± 0.10†	16.8 ± 1.0†
120	0.34 ± 0.01†	0.32 ± 0.05†	8.8 ± 1.3	5.8 ± 1.0	21 ± 2	18 ± 1	6.0 ± 0.8	6.2 ± 0.9	1.03 ± 0.16†	15.6 ± 1.5†
150	0.35 ± 0.02†	0.31 ± 0.05†	9.4 ± 1.5	5.8 ± 1.2	22 ± 2	18 ± 1	6.0 ± 0.6	8.0 ± 0.3	0.95 ± 0.09†	15.7 ± 1.8†
180	0.30 ± 0.01	0.31 ± 0.05	8.4 ± 1.8	6.6 ± 1.2	22 ± 2	17 ± 2	5.2 ± 0.7	7.4 ± 0.7	0.86 ± 0.11†	17.1 ± 2.1†
210	0.31 ± 0.02	0.32 ± 0.07	9.2 ± 1.4	6.0 ± 1.0	20 ± 2	17 ± 2	5.0 ± 0.5	6.4 ± 1.0	0.85 ± 0.13†	17.1 ± 2.1†
240	0.32 ± 0.02	0.30 ± 0.06	9.6 ± 1.8	6.2 ± 1.2	21 ± 2	15 ± 2	4.2 ± 0.6	6.4 ± 0.7	0.98 ± 0.18†	15.0 ± 2.3†
270	0.27 ± 0.01	0.30 ± 0.07	8.6 ± 1.2	6.0 ± 1.2	21 ± 2	17 ± 2	4.4 ± 0.6	8.2 ± 0.7	0.88 ± 0.13†	14.7 ± 2.0†
300	0.29 ± 0.02	0.28 ± 0.04	7.8 ± 1.1	6.0 ± 0.8	20 ± 2	16 ± 1	4.4 ± 0.6	7.4 ± 0.5	0.91 ± 0.16†	13.9 ± 2.8†

* Values are means ± SE; group C, n = 5; group T, n = 5. Abbreviations used are: Q_t, cardiac output; $\overline{PCWP}$, mean pulmonary capillary wedge pressure; $\overline{PAP}$, mean pulmonary artery pressure; $\overline{RAP}$, mean right atrial pressure.

† Significant difference ($p < 0.05$) from control values.

Cardiac output significantly increased during the first 90 minutes of SNP infusion and then decreased so that by 180 minutes of SNP, cardiac output had returned to control levels in both groups; the difference between the two groups was not significant (Table 1). Initial PCWP was slightly higher in group C than in group T, but the difference was not significant; neither thiosulfate nor SNP-induced hypotension (Table 1) produced significant changes in PCWP during 5 hours of anesthesia. Mean pulmonary arterial pressures and right atrial pressures were similar in both groups and remained relatively constant during the infusions of either thiosulfate or saline and SNP (Table 1).

The infusion rate of SNP necessary to maintain the level of arterial hypotension of 60 mm Hg MAP differed markedly between groups as the experiment progressed. The initial infusion rate for both groups, approximately 0.8 mg/min, remained at this level for the duration of the experiment for group T (Fig 2). In contrast, the infusion rate had to be periodically decreased in group C to a final rate of 0.17 ± 0.02 mg/min (8 ± 1 μg/kg/min). Corresponding to the decreasing requirements needed in group C to maintain hypotension was an increasing whole-blood CN level which peaked at 150 minutes and remained high until the end of the infusion (Fig 3). In group T, the whole-blood CN concentration remained consistently less than 40 μg/dl for the duration of the infusion (Fig 3) despite the SNP infusion rate being more than 4 times that of group C by the end of the experiment.

The endogenous plasma thiosulfate concentration, measured before any infusions were given, was similar in both groups (Table 1). In group T, after the bolus injection and 40 minutes of infusion, the plasma

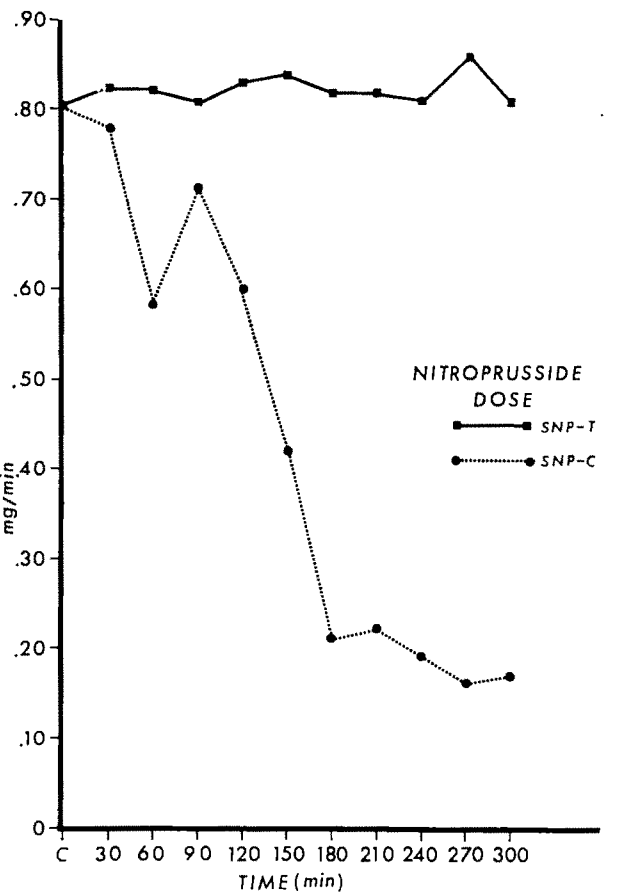


FIG 2. Dose of SNP necessary to maintain hypotension at 60 mm Hg in MAP in test group (SNP-T) and in control dogs (SNP-C) from time 0 to 300 minutes. Doses are significantly different from 120 to 300 minutes ($p < 0.05$).

thiosulfate concentration plateaued at approximately 15.5 mg/dl (Table 1) and remained at this concentration for the duration of the experiment. In contrast,

the control group had a small but significant decrease in endogenous plasma thiosulfate concentration during the first 30 minutes of SNP infusion (Table 1). This decreased level of thiosulfate corresponds to a significant increase in the whole-blood CN concentration (Fig 3). Plasma thiosulfate remained at approximately 0.9 mg/dl in group C (Table 1), whereas whole-blood CN level continued to increase (Fig 3) until it reached 381 ± 44 mg/dl at 150 minutes. When the SNP infusion was decreased, the CN concentration gradually decreased to 304 ± 114 mg/dl at 300 minutes.

Tissue (gracilis muscle) CN determinations were successful in only three samples in each group, which made statistical analysis impracticable. Group T had 45 ± 21 μg/100 g CN, whereas group C had 113 ± 36 μg/100 g. Plasma thiocyanate remained less than the lower limits of thiocyanate assay (1 mg/dl) during the entire time of SNP infusion.

Arterial P_{O_2} remained constant for group T, whereas for group C, Pa_{O_2} increased at various times during the SNP infusion (Table 2) even though ventilation was controlled. Mixed-venous P_{O_2} increased in both groups although the increase was statistically significant only in group C. With one exception arterial and mixed-venous P_{CO_2} were not found to be significantly different from base line in either group (Table 2). Arterial and venous pH values decreased in both groups during SNP infusion, but the decreases were significant in group C only (Table 2), although both groups had received approximately the same amount of bicarbonate during the infusions (Table 2). Urine output was not significantly different between the two groups at any time.

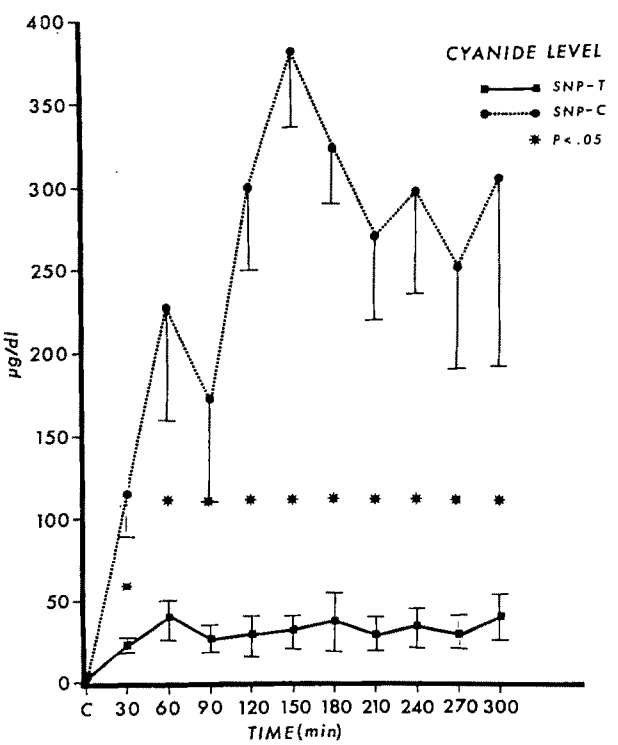


FIG 3. Whole-blood cyanide concentration in test group (SNP-T) and in control dogs (SNP-C) from initial period (C time) through 300 minutes of SNP infusion. Vertical bars are standard error; * denotes significant differences between groups ($p < 0.05$).

Discussion

Controlled deliberate hypotension has proved to be a useful technique for intraoperative homeostasis in anesthetic practice; because of its rapid action, short duration, minimal side effects, and low incidence of tachyphylaxis, SNP has gained wide acceptance as an ideal agent for such hypotension. However, several reports of mortality during its use and the indirect evidence contained in these reports of SNP-induced CN toxicity (3, 10, 11) have led to the recommendation of maximum dosage of 0.5 to 8 μg/kg/min by Ivankovich and colleagues (1) and to 1 to 1.5 mg/kg over 1 to 3 hours, or 0.5 mg/kg/hr for long-term (≥48 hours) administration, by Michenfelder (6) and by Vesey's group (12). However, as noted by Cottrell et al (4) and by Vesey et al (12), variations in response to SNP may occur because of inadequate depth of anesthesia, tachycardia, or interactions with other drugs. Therefore, SNP dosage must be individualized on the basis of response, with careful monitoring for signs of CN toxicity (metabolic acidosis and increased mixed venous P_{O_2}). Michenfelder and Tinker (3) found that these upper limits of dosage apply in dogs as well as in man, adding more evidence to the validity of the canine model for studying SNP toxicity.

The dose of SNP, 0.8 mg/min, used in the present study was relatively large for two reasons: The reduction of arterial blood pressure was greater than is usual in clinical practice, and a light plane of anesthesia was maintained to preserve pressor reflexes. These procedures permitted maximizing the dosage of SNP and achieving maximum blood CN concentrations within a 5-hour period. Metabolic evidence of CN toxicity appears in the dog at approximately the same blood CN concentration as in humans (3, 11, 12), suggesting the applicability of clinical extrapolation.

Detoxification of CN to less toxic thiocyanate requires the mitochondrial enzyme rhodanese (thiosulfate: cyanide sulfurtransferase, EC 2.8.1.1) and a sulfur donor (13). As sufficient rhodanse activity is present in the liver to convert many times the toxic dose of

TABLE 2

Blood-Gas Tensions and pH Values during SNP Infusion in Group C (Saline) and Group T (Thiosulfate)*

Time	Pa_{O_2}		$P\bar{v}_{O_2}$		Pa_{CO_2}		Pv_{CO_2}		pHa		pHv		HCO_3	
	C	T	C	T	C	T	C	T	C	T	C	T	C	T
min				*mm Hg*									*meq*	
0	97±5	89±4	59±3	53±4	35±2	35±2	36±2	41±1	7.33±0.03	7.31±0.02	7.32±0.03	7.26±0.03	8.4±3.4	3.6±3.2
30	94±5	86±4	71±4†‡	50±2	42±2	40±2	48±2†	48±2	7.18±0.05	7.23±0.04	7.15±0.04†	7.23±0.02	10.8±2.7	4.0±3.6
60	105±3‡	83±3	76±5†‡	56±2	35±3	38±2	45±3	45±3	7.16±0.03†	7.25±0.01	7.13±0.03†‡	7.23±0.02	11.8±0.82	14.4±2.4
90	99±7	82±4	73±3†‡	53±4	42±3	39±3	54±4†	45±1	7.14±0.04†	7.24±0.02	7.05±0.04†	7.23±0.02	17.0±1.8	8.7±3.4
120	105±7‡	80±6	73±5†‡	57±2	41±4	40±3	52±7	46±3	7.08±0.07†‡	7.21±0.02	7.09±0.05†	7.20±0.02	18.0±3.9	12.2±3.1
150	93±9	85±2	60±11	61±4	43±3†	40±2	53±4	49±4	7.07±0.05†‡	7.22±0.03	7.06±0.04†‡	7.19±0.03	14.0±7.4	13.2±1.6
180	105±5†	86±2	64±8	59±3	42±2	41±4	53±6	53±4	7.13±0.05†	7.24±0.04	7.11±0.05†	7.21±0.04	17.0±4.4	12.0±3.4
210	112±11	90±2	80±10	60±4	40±2	34±2	54±5†	45±1	7.11±0.03†	7.23±0.03	7.09±0.03†‡	7.21±0.03	14.4±3.1	14.0±2.2
240	109±14	89±2	64±15	59±4	38±3	34±2	44±9	42±1	7.16±0.03†	7.26±0.03	7.09±0.2†‡	7.24±0.03	16.4±3.7	14.0±3.6
270	109±14	87±2	66±15	59±4	39±2	35±2	48±7	48±2	7.17±0.04	7.24±0.03	7.12±0.02†	7.22±0.04	10.0±4.0	14.0±3.6
300	111±11	87±2	64±17	61±5	41±2	39±2	44±8	47±2	7.18±0.03	7.20±0.06	7.14±0.04†	7.16±0.06	6.40±3.7	6.0±6.0

* Values are means ± SE.
† $p < 0.05$ compared with control group.
‡ $p < 0.05$ between groups.

CN to thiocyanate, the rate-limiting factor in the reaction appears to be availability of a sulfur donor. Thiosulfate can be utilized as the sulfur donor both in vitro (14) and in vivo (15) and as a substrate for the isolation and purification of rhodanse (16–18), but the endogenous sulfur donor for this enzyme is unknown. Thiosulfate has been isolated in urine (19) and appears to be an endogenous intermediate product of sulfur-containing amino-acid metabolism (20). The kidney can transport thiosulfate in either direction at low concentrations (21) but the feedback regulation of the metabolism and excretion of this substance is unknown. Utilizing a specific assay, we have found the thiosulfate concentration in both human and dog plasma to be approximately 1 mg/dl, and approximately 3 mg/day is excreted in humans (Ivankovich AD, Braverman B, Shah G. Thiosulfate metabolism and its relation to cyanide detoxification. Paper presented at the 53rd Congress of the International Anesthesia Research Society, March 11–15, 1979, Hollywood, Florida). Therefore, thiosulfate is a naturally occurring, endogenous substance that should not produce adverse side effects when used clinically.

Administration of sodium nitrite followed by sodium thiosulfate has been an accepted antidotal procedure for acute CN poisoning since the classic studies by Chen and associates (15). However, clinicians are now confronted by a situation quite different from that seen in acute CN toxicity, as the deliberate administration of SNP results in slow, progressive CN accumulation in blood and tissue in a manner giving only a subtle appearance of the symptoms of acute toxicity. In a previous study (5), we showed that a thiosulfate infusion, by itself, is capable of providing excellent prophylaxis against CN infusion when administered simultaneously; tissue accumulation and expansion of the CN "pool" was not observed, as with other antidotes. A bolus intravenous injection of the therapeutic dose of the 150 mg/kg (15) was not effective in providing such protection against a CN infusion. From this we concluded that high plasma concentrations of thiosulfate are necessary for rapid CN detoxification. Thiosulfate is rapidly eliminated by the kidneys and has a metabolic half-life of only 23 minutes in man after administration by a bolus intravenous injection. Although the total dose of thiosulfate used in this study, 180 mg/kg, was close to the therapeutic dose, the bolus injection of 30 mg/kg followed by the constant infusion of 30 mg/kg/hr for 5 hours was effective in maintaining a constant plasma concentration of 15.5 mg/dl and in preventing CN toxicity. If CN or CN-producing compounds are continuously infused, plasma thiosulfate can also easily be maintained at high concentrations by continuous infusion.

The endogenous thiosulfate concentration measured in this study, approximately 1 mg/dl, was inadequate to detoxify the significant amounts of CN from metabolized SNP. The thiosulfate-treated dogs received a total dose of 0.73 mM/kg ($Na_2S_2O_3 \cdot 5H_2O$; mol wt = 248.11) and the total dosage of SNP delivered, approximately 12 mg/kg for a 20-kg dog, was equivalent to 0.04 mM/kg (SNP mol wt = 297.97). The molar ratio of total doses was approximately 18:1, which would appear to be more than adequate to detoxify the 0.2 mM of CN potentially liberated from the SNP. But, because of its rapid renal excretion, thiosulfate is not stored nor does it accumulate in the body. Hence the available thiosulfate is equivalent to the plasma concentration, 15.5 mg/dl, times the vol-

ume of distribution, 195 ml/kg, or approximately 0.12 mM/kg; 0.08 mM/kg (100 μg/kg) of CN are not detoxified. If we assume that most of the CN remains in the extracellular compartment and has the same volume of distribution as thiosulfate, then the whole-blood CN concentration should be approximately 50 μg/dl, which is in agreement with our measured value of 40 μg/dl.

Michenfelder and Tinker (3) used a similar method of thiosulfate administration with a larger dose of SNP delivered over a 24-hour period. Whole-blood CN concentrations remained less than 20 μg/dl in their study, but hemodynamic parameters were not closely followed and blood pressure was not maintained at hypotensive levels. These authors noted severe volume depletion after 48 hours of SNP and thiosulfate infusion, which probably impaired renal function, decreased thiosulfate excretion, and increased the available plasma thiosulfate concentration. Although we did not observe similar volume depletion during our relatively brief study, the osmotic diuretic potential of thiosulfate may lead to a risk of patient dehydration which should not be overlooked. The increase in plasma thiosulfate presumably resulted in the lower CN levels measured. In a second study (22), Tinker and Michenflder showed that the SNP tolerance limits increased during renal failure in dogs, presumably the result of thiosulfate conservation. The normal concentration of whole-blood CN in humans is up to 15 μg/dl in smokers; the lethal range is greater than 500 μg/dl (7). Therefore, the dosage and method of thiosulfate administration utilized in our study and in those cited above were effective in rapidly detoxifying CN derived from metabolized SNP and in maintaining whole-blood CN levels well below the toxic range. In addition, thiosulfate infusion prevented significant tissue CN accumulation in the limited number of samples analyzed.

Another CN antidote, hydroxocobalamin, readily combines with CN to form cyanocobalamin (vitamin B_{12}). It has been shown to provide good prophylaxis against therapeutic doses of SNP in man and against toxic levels in primates (23). However, when dogs were given an infusion of hydroxocobalamin and CN, high doses of hydroxocobalamin were required to prevent CN lethality, CN accumulation in tissues was observed, and cardiovascular parameters were not favorably maintained. This lack of potency, limited shelf-life, and high expense make hydroxocobalamin a less suitable antidote and adjuvant for SNP-induced CN toxicity than thiosulfate.

Tachyphylaxis or resistance to the hypotensive effects of SNP has been previously reported (24) with the presumption that it may have been produced by an inability to detoxify CN. In our control animals, the requirements for SNP to maintain hypotension markedly decreased during the 5-hour period, which could be explained by diminished cardiac reserve due to CN toxicity. During this time, the endogenous thiosulfate level decreased and the whole-blood CN concentration increased to lethal levels. In the thiosulfate-treated group, the requirements for SNP to maintain the prescribed degree of arterial hypotension remained practically constant over the 5-hour period. Neither group of animals demonstrated tachyphylaxis or resistance to SNP. We previously reported that pretreatment of dogs with CN failed to antagonize the hypotensive effects of SNP (25). The present study supports our earlier conclusions, that the reported resistance or tachyphylaxis to SNP is not the result of liberated CN, as has been proposed by Grayling et al (26). Depth of anesthesia and baroreceptor reflexes appear to be the important factors when untoward reactions to SNP are observed clinically.

Recently, a case was presented (27) in which a patient received 0.6 mg/min of SNP for 4 days. On the third day, the patient was found to have a dangerously high whole-blood CN concentration. Sodium thiosulfate was infused at 5 times the molar concentration of SNP and the blood CN concentration decreased over the next several hours. The authors noted that thiosulfate did not reduce the effectiveness of SNP in decreasing the patient's blood pressure.

In summary, the present study demonstrates that thiosulfate, administered in a dose of 30 mg/kg followed by a constant infusion of 30 mg/kg/hr, provides excellent protection against CN toxicity during 5 hours of SNP-induced hypotension in dogs. In addition to its ability to detoxify CN rapidly, thiosulfate administration did not appear to produce deleterious side effects and was not antagonistic to the desired hemodynamic effects of nitroprusside. Sodium thiosulfate is suggested as a safe and effective prophylactic adjuvant for sodium nitroprusside.

REFERENCES

1. Ivankovich AD. Nitroprusside and other short-acting hypotensive agents. Int Anesthesiol Clin 1978;16:1–318.
2. Tinker JH, Michenfelder JD. Sodium nitroprusside: pharmacology, toxicology and therapeutics. Anesthesiology 1976;45: 340–54.
3. Michenfelder JD, Tinker JH. Cyanide toxicity and thiosulfide protection during chronic administration of sodium nitroprusside in the dog. Correlation with a human case. Anesthesiology 1977;47:441–8.

4. Cottrell JE, Casthely P, Brodie JD, Patel K, Klein A, Turndorf H. Prevention of nitroprusside-induced cyanide toxicity with hydroxocobalamin. N Engl J Med 1978;298:809-11.
5. Ivankovich AD, Braverman B, Kanuru RP, Heyman HJ, Paulissian R. Cyande antidotes and methods of their administration in dogs: a comparative study. Anesthesiology 1980;52:210-6.
6. Michenfelder JD. Cyanide release from sodium nitroprusside in the dog. Anesthesiology 1977;46:196-201.
7. Feldstein M, Klendshoj HC. Determination of cyanide in biologic fluids by micro-diffusion analysis. J Lab Clin Med 1954;44:166-70.
8. American National Standard methylene blue method for measuring residual chemicals in films, plates, and papers. American National Standard Insitute. Ph 4.8, 1971.
9. Winner BJ. Statistical principles in experimental design. 1st ed. New York: McGraw-Hill, 1972:298-318.
10. Davies DW, Greiss L, Kadar D, Steward DJ. Sodium nitroprusside in children: observations on metabolism during normal and abnormal responses. Can Anaesth Soc J 1975;22:553-60.
11. Davies DW, Kadar D, Steward DJ, Munro IR. A sudden death associated with the use of sodium nitroprusside for induction of hypotension during anesthesia. Can Anaesth Soc J 1975;22: 547-52.
12. Vesey CJ, Cole PV, Simpson PJ. Cyanide and thiocyanate concentrations following sodium nitroprusside infusion in man. Br J Anaesth 1976;48:651-60.
13. Land K. Die Rhodanbildung im Tierkorper. Biochem Z 1933;250:243-56.
14. Saunders JP, Himwich WA. Properties of the transulfurase responsible for the conversion of cyanide to thiocyanate. Am J Physiol 1950;163:404-9.
15. Chen KK, Rose CL, Clorves GHA. Comparative values of several antidotes in cyanide poisoning. Am J Med Sci 1934;188: 767-81.
16. Sorbo BH. Crystalline rhodanese. I. Purification and physiochemical examination. Acta Chem Scand 1953;7:1129-36.
17. Horowitz PM. Purification of thiosulfate sulfurtransferase by selective immobilization on blue agarose. Anal Biochem 1978;86:751-3.
18. Horowitz PM, Patel K. Some comparisons between solution and crystal properties of thiosulfate sulfurtransferase. Biochem Biophys Res Commun 1980;94:419-23.
19. Fromageot C, Royer A. La Presence constante du thiosulfate dans l'urine des animaux superieurs et sa signification physiologique. Enzyme 1943-45;7:361-72.
20. Kun E. The metabolism of sulfur-containing compounds. In: Greenberg DM, ed. Metabolic pathways. New York: Academic Press, 1961:237-59.
21. Ulrich KJ, Rumrich G, Klass S. Bidirectional active-transport of thiosulfate in the proximal convolution of the rat kidney. Pfluegers Arch 1980;387:127-32.
22. Tinker JH, Michenfelder JD. Increased resistance to nitroprusside-induced cyanide toxicity in anuric dogs. Anesthesiology 1980;52:40-7.
23. Posner MA, Rodkey FL, Tobey RE. Nitroprusside-induced cyanide poisonings: antidotal effect of hydroxocobalamin. Anesthesiology 1976;44:330-5.
24. Greiss L, Tremblay NAG, Davies DW. The toxicity of sodium nitroprusside. Can Anaesth Soc J 1976;23:480-5.
25. Braverman B, Ivankovich AD, Lavine LM, Klowden AJ. Failure of cyanide to antagonize sodium nitroprusside in vivo in dogs. Anesth Analg 1980;59:672-7.
26. Grayling GW, Miller ED, Peach MJ: Sodium cyanide antagonism of the vasodilator action of sodium nitroprusside in the isolated rabbit aortic strip. Anesthesiology 1978;49:21-5.
27. Schulz V, Bonn R, Kammerer H, Kriegel R, Ecker N. Counteraction of cyanide poisoning by thiosulfate when administering sodium nitroprusside as a hypotensive treatment. Klin Wochenschr 1979;57:905-7.

ANESTH ANALG
1982;61:127-9

Uterine Contractions and the Spread of Local Anesthetics in the Epidural Space

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SIVAKUMARAN, C., RAMANATHAN, S., CHALON, J., AND TURNDORF, H.: Uterine contractions and the spread of local anesthetics in the epidural space. Anesth Analg 1982;61:127-9.

Local anesthetics injected into the epidural space during a uterine contraction are commonly believed to produce a higher than usual level of anesthesia. This was evaluated in 34 parturients undergoing continuous lumbar epidural labor analgesia. The patients were divided into two equal groups. In group A, the inducing dose (2% chloroprocaine, 8 ml) was injected during an active uterine contraction and the top-up dose was injected between contractions. In group B, the injection sequence was reversed. Irrespective of the time of injection, in relation to uterine contractions, approximately 16 dermatomal segments were blocked in both groups. It is concluded that uterine contractions do not affect spread of local anesthetic solution in the epidural space.

Key Words: ANESTHESIA: obstetric; ANESTHETIC TECHNIQUES: epidural.

IT HAS BEEN shown that the base line epidural pressure is greater (than in nonpregnant patients) during obstetric labor with intermittent peak increases with each uterine contraction (1). This is attributed to engorgement of epidural veins and maternal skeletal muscular activity. This has led to the belief that local anesthetics injected into the epidural space during uterine contractions may produce a high level of anesthesia (2). The purpose of this study was to test the validity of this clinical impression.

Methods

Thirty-four full-term primiparous healthy patients scheduled for epidural labor analgesia were subjects for the study. The protocol was approved by the Committee on Human Experimentation of the New York University Medical Center. All patients gave informed consent for the study. None of the subjects had any spinal deformity. The vertex was the presenting part in all instances. Vital statistics of the patients were: mean age, 31 ± 5 (SD) years (range 26 to 36 years); mean height, 164 ± 12 (SD) cm (range 150 to 166 cm); mean weight, 71 ± 12 (SD) kg (range 67 to 85 kg).

Patients were divided into two equal groups, A and B. In group A, following intravenous infusion of 800 ml of Hartman's solution, a Portex catheter (Portex Co, Quincy, MA) was inserted into the epidural space through the L3-4 interspace and advanced 2 cm cephalad. The cervix was 4 to 5 cm dilated with the presenting part at station 0 to −1. Maternal blood pressure (measured by Van Recklinghausen's method) and heart rate (HR) were recorded. Mean blood pressure ($\overline{BP}$) was calculated as diastolic pressure plus one third the pulse pressure. Uterine contractions were monitored continuously by tocodynamometry.

The inducing dose of 8 ml of 2% chloroprocaine was injected at a rate of 1 ml/sec during a uterine contraction, with patients lying supine with a single pillow. The injection was started when the ascending portion of the tocodynamometric tracing had reached 40% to 50% of its final height (as assessed by the recorded peak heights of the three preceding waves, Fig 1). Left uterine displacement was instituted 5 minutes after the injection. An anesthesiologist who was not familiar with the nature of the study assessed sensory blockade by pinprick. Dermatomal distribution of altered sensation was sought for in both the anterior and posterior aspects of the body (3). If there

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Received from the Department of Anesthsiology, New York University Medical Center, 550 First Avenue, New York, New York 10016. Accepted for publication September 24, 1981.
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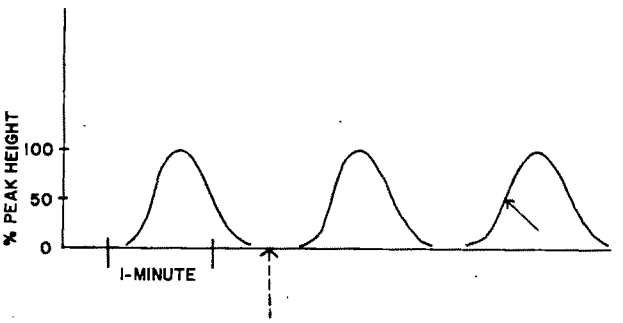


FIG 1. Time of epidural injection in relation to uterine contractions, shown as tocodynamometric tracings. Interrupted arrow represents injection made during interval between uterine contractions. Solid arrow represents injection started when contraction wave reached approximately 40% of peak height. Sequence of injections depicted in this figure was used in patients in group B.

was a discrepancy in the number of blocked segments between the left and right sides of the body, the segments were counted separately on each side and their mean was used as the final level of block. Blockade was assessed at 5-minute intervals and considered complete when two consecutive measurements (5 minutes apart) failed to reveal any additional spread. All affected thoracic, lumbar, and sacral segments were counted; coccygeal segments were excluded. Blocked segments were plotted on a dermatome chart (Fig 2).

The block was allowed to wear off completely (which took 75 ± 3 minutes, ±1SD) as evidenced by return of painful contractions, complete recovery of somatic motor function, and normal pinprick sensation. The top-up dose was then injected during the interval between uterine contractions (Fig 2). Chloroprocaine volume and concentration, rate of injection, and patient position were identical with those used for the first injection. Sensory level was evaluated as noted above. The cervix was 5 to 6 cm dilated with the presenting part at station 0 to +1.

In group B, the protocol was similar to that in group A except that the first injection was made during the interval between two uterine contractions and the second during a uterine contraction. The interval between the injections was 77 ± 7 minutes. The progression of labor and the descent of the presenting part during the two injections were similar to those in group A.

Total number of segments blocked, and changes in maternal $\overline{BP}$ and HR obtained after the first injection were compared with those obtained after the second in each group by the t-test at levels of significance of $p < 0.05$.

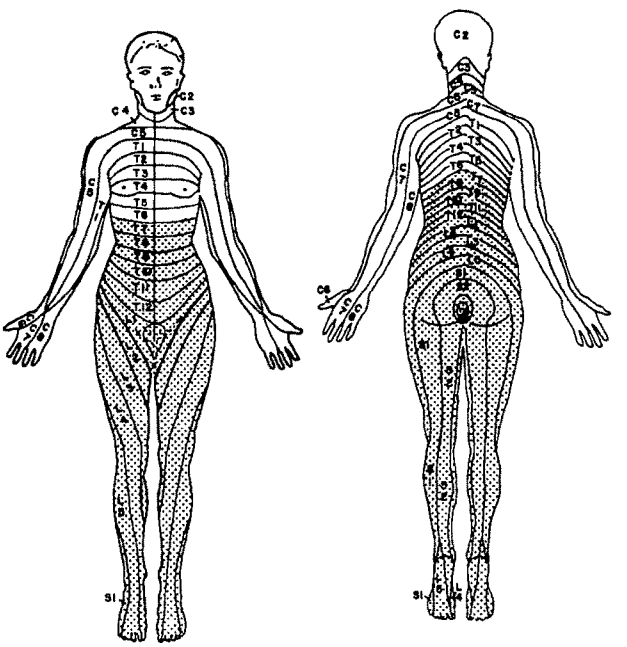


FIG 2. Dermatome chart used to mark blocked segments (dotted areas) in anterior and posterior aspects of body. Injection of 8 ml of 2% chloroprocaine produced an epidural block extending to seventh thoracic dermatome, irrespective of time of injection, during or between contractions.

Results

In group A, the first injection (during contraction) blocked 16.7 ± 0.44 (±1 SE) segments and decreased $\overline{BP}$ by 4 ± 2 torr and HR by 2 ± 2.5 beats per minute (Table). The top-up dose (between contractions) blocked 16.6 ± 0.46 segments, and decreased $\overline{BP}$ by 5 ± 2 torr and HR by 3 ± 2 beats per minute. In group B (reversed injection sequence), the first injection blocked 16.2 ± 0.44 segments and reduced $\overline{BP}$ and HR by 4 ± 1 torr and 3 ± 1 beats per minute, respectively. The second injection blocked 16.4 ± 0.43 segments and decreased the $\overline{BP}$ and HR by 5 ± 1 torr and 1 ± 2 beats per minute, respectively. There was no statistically significant difference in any of the measurements between the two injections in both groups.

Discussion

Our results indicate the uterine contractions do not significantly affect the spread of local anesthetics in the epidural space. Irrespective of the time of injection, in relation to uterine contractions, 8 ml of 2% chloroprocaine blocked approximately 16 dermatomes. Because of similar changes in maternal $\overline{BP}$ and HR, the autonomic blockades produced by the two injections can also be considered almost identical with

TABLE

Number of Anesthetized Segments and Changes in Maternal Blood Pressure and Heart Rate in Patients in Groups A and B*

Parameter	Group A (n = 17)		Group B (n = 17)	
	A-I	A-II	B-I	B-II
Segments blocked	16.7 ± 0.44	16.6 ± 0.46	16.2 ± 0.44	16.4 ± 0.43
Decrease in $\overline{BP}$ (torr)	4 ± 2	5 ± 2	4 ± 1	5 ± 1
Decrease in HR (beats/min)	2 ± 2.5	3 ± 2	3 ± 1	1 ± 2

* Values are means ± 1 SE of data from 17 patients. Abbreviations used are: A-I, first epidural injection in group A during a uterine contraction; A-II, top-up (or second) injection made between contractions; in group B, sequence of injections was reversed; $\overline{BP}$, mean blood pressure; HR, heart rate. In all instances p values were not significant.

each other. The experimental design used in our study enabled us to compare the two injections in the same patient. It was, therefore, unlikely that anatomic or other patient variables could have influenced our results. We did not use the same sequence of injections in all our patients. In group A, the first dose was injected during a contraction and the second dose between contractions. In group B, the sequence was reversed. This diminished the likelihood of the first dose contributing to the effects produced by the second one. This could only happen when the two doses followed each other in a fixed sequence in all the patients.

The failure of uterine contractions (which reduce the compliance of the epidural space) to affect the spread of local anesthetics in the epidural space may be due to several factors. The epidural space is not a closed sac. It freely communicates with paravertebral areas (4). Contrast media injected into the lumbar epidural space have been shown to spread laterally in 80% of patients 25 to 35 years of age (5). Sharrock and Greenidge (5) noted that in full-term pregnant patients the volume of local anesthetic required to block one segment (segmental dose requirement, SDR) increased with increasing volumes of local anesthetics. For example, they noted that 5 ml of the local anesthetic blocked approximately 10 segments (SDR = 0.5 ml), but with a 25-ml dose, only approximately 20 segments were blocked (SDR = 1.25 ml). The failure of the larger dose to produce a more extensive block may have been due to escape of local anesthetics into the paravertebral space through the intervertebral foramina. A similar lateral escape of local anesthetics injected into the epidural space during a contraction may partly explain our findings.

The SDR in our study was also 0.5 ml. The lower SDR seen during pregnancy is attributed to mechanical obliteration of the epidural space by engorged veins. A similar reduction in the epidural space compliance associated with uterine contractions is also believed (without proof) to facilitate spread of local anesthetics. However, it has been shown that SDR is reduced by 30% even as early as 8 to 12 weeks of gestation when such mechanical factors are unlikely to play a role (7). It is possible, therefore, that changes in epidural space compliance do not significantly alter local anesthetic dissemination. Consequently, it is not surprising that the uterine contractions, which only transiently diminish epidural space compliance, had little effect on the dispersion of local anesthetics in our study.

REFERENCES

1. Galbert MW, Marx GF: Extradural pressure in the parturient patient. Anesthesiology 1974;40:499–502.
2. Bromage PR. Epidural analgesia. Philadelphia: WB Saunders, 1978:546.
3. Bromage PR. Aging and epidural dose requirement. Br J Anaesth 1969;41:1016–21.
4. Macintosh RR, Mushin MW. Observations on the epidural space. Anaesthesia 1947;2:100–3.
5. Burn JM, Guyer PB, Langdon L. The spread of solutions injected into the epidural space. Br J Anaesth 1973;45:338–44.
6. Sharrock NE, Greenidge J. Epidural dose responses in pregnant and nonpregnant patients. Anesthesiology 1979;51:S298.
7. Fagraeus L, Urban BJ, Gross AM, Bromage PR. Spread of epidural analgesia in early pregnancy. Anesthesiology 1979;51: S299.

ANESTH ANALG
1982;61:130-2

Oral Ranitidine for Prophylaxis against Mendelson's Syndrome

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FRANCIS, R. N., AND KWIK, R.S.H.: Oral ranitidine for prophylaxis against Mendelson's syndrome. Anesth Analg 1982;61:130-2.

The effect of the new H_2 receptor antagonist ranitidine on gastric pH was studied using a double-blind technique in 36 patients undergoing elective surgery, 18 of whom were given 150 mg of ranitidine orally the night before and on the morning of surgery. The incidence of gastric residue pH higher than 2.5 ($p < 0.01$) was significantly greater in patients given ranitidine than in 18 untreated control patients. The mean volume of gastric aspirate in the treated group as 6.7 ml (range 2 to 20 ml) compared with the control group 15.6 ml (range 2 to 44 ml). The higher potency, longer duration of action, and fewer side effects of ranitidine compared with cimetidine suggest that this drug may have clinical advantages over other H_2 receptor antagonists.

Key Words: PHARMACOLOGY: ranitidine; GASTROINTESTINAL TRACT: stomach; RECEPTORS: H_2.

PULMONARY aspiration of gastric contents is a recognized hazard associated with anesthesia in both surgical and obstetric patients. It may also occur after surgery and in the debilitated and comatose patient. Mendelson stressed the importance of the acid content of the aspirate in producing pulmonary injury. He described a syndrome, now referred to as Mendelson's syndrome, which occurs in obstetric patients following gastric acid aspiration (1). Volumes of gastric juice as little as 25 ml and gastric pH levels less than 2.5 will generally produce severe pulmonary damage (2, 3). The mortality reported following gastric aspiration varies from 25% to 100% (4, 5).

The prophylactic use of antacids before surgery seems to be a logical method of combating Mendelson's syndrome (6). The efficacy of antacids has, however, been questioned (7) and pulmonary aspiration of antacids alone may itself lead to severe pulmonary damage (8).

Ash and Schild (9) postulated the existence of more than one type of histamine receptors. Histamine H_1 receptors are present in arterial, intestinal, and bronchial smooth muscles. These receptors are antagonized by the classic antihistamines. The other actions of histamine are stimulation of the heart muscle and gastric secretion. These effects are blocked by histamine H_2 receptor antagonists, metiamide and cimetidine (10). Ranitidine is a new histamine H_2 receptor antagonist. Its chemical name is N-[2-[[[5-[(dimethyl amino)methyl]-2-furanyl]methyl]thio]ethyl]-N'-methyl-2-nitro-1,1-ethenediamine hydrochloride. The empirical formula is $C_{13}H_{22}N_4O_3S \cdot HCl$ with a molecular weight of 350.87 and a solubility well in excess of 20% in water. The elimination half-life after an oral dose of 150 mg of ranitidine was found to be between 4 to 8 hours in five subjects (11).

This paper evaluates the effectiveness of ranitidine in inhibiting gastric acid production in patients undergoing elective surgery.

Methods

Thirty-six healthy adult patients (range 17 to 65 years, mean 34 years) undergoing elective surgery and requiring tracheal intubation, were selected for a double-blind study. Patients received either ranitidine, 150 mg, or a placebo orally with a small amount of water, according to a predetermined randomization code at 10 p.m. the night before and 6 a.m. on the day of surgery. The patients fasted from midnight on. Premedication consisting of diazepam, 10 mg, by intramuscular injection was given approximately 1 hour before surgery.

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All patients were anesthetized using a standardized technique. Intravenous induction with thiopental, 3 to 5 mg/kg, was followed with succinylcholine, 1 mg/kg, and the patient was briefly oxygenated until muscle paralysis occurred. Tracheal intubation was performed and anesthesia was maintained with nitrous oxide, oxygen, and enflurane. A nasogastric tube was inserted into the stomach, and the contents were aspirated. Patients were tilted from side to side and placed head-down whenever possible to aid gastric aspiration.

The volume of gastric aspirate and sampling times were recorded. The pH of the sample was measured using a Corning digital 112 research pH meter unless the sample was too small, in which case pH indicator paper was used. Mean pH was calculated using logarithmic numbers rather than actual hydrogen ion concentrations.

Informed written consent was obtained from all patients, and the study was approved by the Hospital Research Protocol Committee.

Results

The pH levels of gastric aspirate in control patients and in patients treated with ranitidine are shown in Fig 1. Analysis of the results is shown in the Table. In four of the 18 patients given ranitidine, no gastric sample could be obtained. In 13 of 14 patients treated with ranitidine (93%) in whom a sample was obtained, the pH was greater than 2.5. This was statistically significantly ($p < 0.01$) more frequent than in control patients in whom only seven of 18 patients (34%) had a pH greater than 2.5. The distribution of pH values with respect to time after the second dose of ranitidine is shown in Fig 2. Only one of 14 patients failed to achieve a pH greater than 2.5. This high pH was seen up to 8½ hours after the morning dose of ranitidine. The mean volume of gastric aspirate in the treated group was 6.7 ml (range 2 to 20 ml) compared with the control group, 15.9 ml (range 2 to 44 ml). The difference is statistically significant ($p < 0.02$).

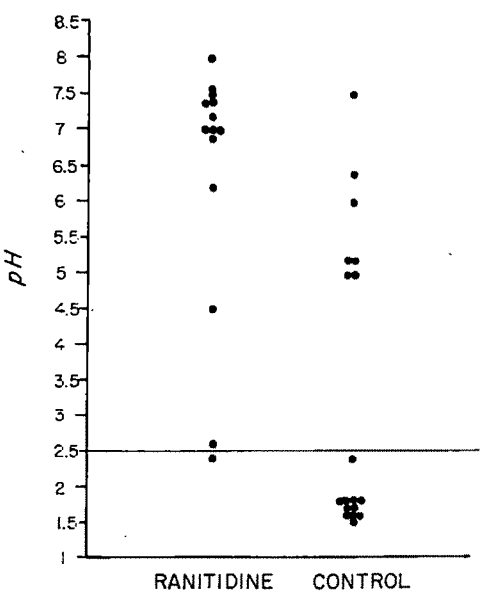


FIG 1. Distribution of pH values of gastric aspirate in control patients and in patients treated with ranitidine.

Discussion

Ranitidine is a new highly selective H_2 receptor antagonist which, when given orally, produces profound and sustained inhibition of gastric acid secretion (12). The present study showed that ranitidine, 150 mg, given orally the night before and on the morning of surgery was an effective regimen for elevating the pH of gastric juice. Only one of 14 patients failed to achieve a pH greater than 2.5. In

TABLE

pH and Volume of Gastric Residue*

	N	pH†	Volume‡	No. of patients with pH > 2.5§
			ml	
Placebo	18	3.3 ± 2.1	15.9 ± 14.35	7/18
Ranitidine	18	6.3 ± 1.8	6.7 ± 6.6	13/14

* Values are means ± SD.
† $p < 0.001$, *t*-test.
‡ $p < 0.02$, *t*-test.
§ $p < 0.01$, chi-square.

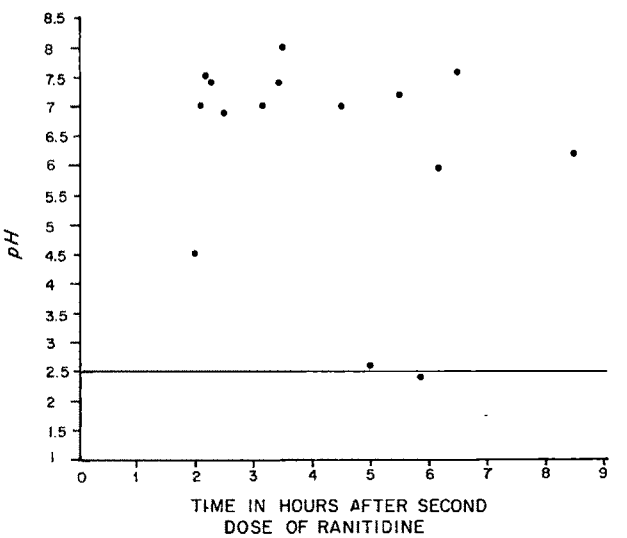


FIG 2. Distribution of gastric aspirate pH in patients treated with ranitidine with respect to time after second dose.

patients given ranitidine, gastric aspiration was unsuccessful in four patients and in the 14 patients in whom a sample was obtained, the mean volume was less than in the control group. The high pH was observed up to 8½ hours after the morning dose of ranitidine. The evening dose inhibits gastric acid secretion during the night. This produces an increase in gastric pH which is maintained throughout most of the day by the morning dose. Protection from acid pulmonary aspiration, therefore, can be achieved in most patients at the time of induction of anesthesia and during the immediate postoperative recovery period by administration of ranitidine on the evening before and again on the morning of elective surgery. The drug was well tolerated by patients and no adverse reactions were observed.

The time of onset of ranitidine may well be relatively short as peak plasma concentrations following oral intake of ranitidine have been reported within 30 minutes in some patients (11). Ranitidine may thus be effective when given to patients scheduled for emergency surgery. The duration of action of 150 mg of ranitidine taken orally has been shown to last for more than 9 hours (13) compared with 4 to 6 hours with cimetidine. On a molar basis, ranitidine is 4 times more potent than cimetidine in inhibiting pentagastrin-stimulated gastric acid secretion (14). Central nervous system side effects consisting of confusion and psychiatric disorders as well as endocrine side effects consisting of lactation, gynecomastia, and impotence reported with cimetidine are not seen with ranitidine (15–17).

The authors believe that ranitidine may thus have sufficient clinical advantages over other available H_2 receptor antagonists to warrant further clinical trials.

ACKNOWLEDGMENTS

The authors wish to acknowledge the cooperation of the medical and nursing staff at the King Faisal Specialist Hospital and Research Centre, R. Ancheta, Dr. N. L. Perrin, and Glaxo Group Research, Ltd. for assistance in preparing this investigation and supplying ranitidine.

REFERENCES

1. Mendelson CC. The aspiration of stomach contents into the lungs during obstetric anesthesia. Am J Obstet Gynecol 1948;52:191–204.
2. Roberts RB, Shirley MA. Reducing the risk of acid aspiration during cesarean section. Anesth Analg 1974;53:859–68.
3. Teabeaut JR. Aspiration of gastric contents: experimental study. Am J Pathol 1952;28:51–62.
4. Cameron JL, Mitchell WH, Zuidema GD. Aspiration pneumonia, clinical outcome following documented aspiration. Arch Surg 1973;106:49–52.
5. Lewis RT, Burgess JH, Hampson LS. Cardiorespiratory studies in critical illness. Arch Surg 1971;103:335–40.
6. Taylor G, Pryse-Davies J. The prophylactic use of antacids in the prevention of the acid-pulmonary-aspiration syndrome (Mendelson's syndrome). Lancet 1966;1:288–91.
7. Moir DD. Editorial: Mendelson's syndrome. Br J Anaesth 1980;52:1–3.
8. Gibbs CP, Schwartz DJ, Wynne JW, et al. Antacid pulmonary aspiration in the dog. Anesthesiology 1979;51:452–3.
9. Ash ASF, Schild HO. Receptors mediating some actions of histamine. Br J Pharmacol 1966;27:427–39.
10. Black JW, Duncan WAM, Durant CJ, Gavellin CR, Parsons EM. Definition and categorism of histamine-H_2 receptors. Nature (Lond) 1972;236:385–90.
11. McFayden ML, Folb PI, Marks IN, Wright JP, Lucke W. The pharmacokinetics of ranitidine in patients with chronic duodenal ulceration. Scand J Gastroenterol [Suppl] (in press 1981)
12. Peden NR, Saunders SHB, Wormsley KG. Inhibition of pentagastrin-stimulated and nocturnal gastric secretions by ranitidine. Lancet 1979;1:690–2.
13. Dammann HG, Kather H, Augustin HJ, Simon B. Untersuchung uber die wirkungsdauer von ranitidin. Dtsch Med Wochenschr 1980;105:603–5.
14. Domschke W, Lux G, Domschke S. Gastric inhibitory action of H_2 antagonists and cimetidine. Lancet 1979;1:320.
15. Walt RP, Richardson JW, Oehr T, Misiewicz JJ. Ranitidine and the blood-brain barrier. Scand J Gastroenterol (Suppl) (in press 1981).
16. Nelis GF, Van de Meene JGC. Comparative effect of cimetidine and ranitidine in prolactin secretion. Postgrad Med J 1980;56: 478.
17. Mignon M, Vallot Th, Mayeur S, Bon Fils S. Ranitidine and cimetidine in Zollinger-Ellison syndrome. Br J Pharmacol 1980;10:173–4.

ANESTH ANALG
1982;61:133-7

A Clinical Double-Blind Study of Dibucaine and Tetracaine in Spinal Anesthesia

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ROCCO, A. G., FRANCIS, D. M., WARK, J. A., CONCEPCION, M. A., AND COVINO, B. G.: A clinical double-blind study of dibucaine and tetracaine in spinal anesthesia. Anesth Analg 1982;61:133-7.

The effects of 0.25% dibucaine and 0.5% tetracaine used for the production of spinal anesthesia were compared in 30 healthy surgical patients. Fifteen patients were assigned to each of the two agents using a randomized, observer and patient-blinded method. Success rate, times of onset and regression of analgesia, intensity of motor blockade, and cardiovascular effects were assessed and the results were analyzed statistically. There were no differences in success rate, in latency, or in duration of action between the two spinal anesthetic agents. Tetracaine was found to be associated with a significantly greater decrease in arterial pressure and more complete motor blockade.

Key Words: ANESTHETIC TECHNIQUES: spinal; ANESTHETICS, Local: dibucaine, tetracaine.

DIBUCAINE, a substituted amide of quinoline was synthesized by Miescher in 1925 and introduced clinically for spinal anesthesia by Howard Jones in 1930 (1). He used hypobaric dibucaine, whereas Silverton (2) first described the use of hyperbaric solutions in 1934. Tetracaine, synthesized in 1928 by Eisleb, is a derivative of para-aminobenzoic acid and its clinical debut as a spinal anesthetic agent was reported by Sise in 1935 (3), using a hyperbaric technique. Following these initial reports, numerous workers have described spinal techniques utilizing dibucaine and tetracaine. Each agent has become known by different names in various parts of the world (Table 1). Tetracaine has become the most commonly used spinal anesthetic agent in the United States, whereas dibucaine is the only agent commercially available for spinal anesthesia in the United Kingdom and other European countries where the use of spinal anesthesia is more limited.

In 1949 Roman and Adriani (4) reported the results of more than 5000 cases of spinal anesthesia using hyperbaric dibucaine and, incidently, compared some of their findings with those obtained in 836 cases who received tetracaine. They found no significant difference in either the nature or in the incidence of complications between the two agents. However, no indication of the dose of tetracaine used was given nor were data comparing the efficacy of the two drugs presented. Moreover the study was not a controlled comparison. Despite the long-term use of these two agents, no controlled studies to determine the comparative efficacy of tetracaine and dibucaine following subarachnoid administration in man have been published. One of the difficulties in attempting such a study is to ensure that equipotent doses of the two agents are utilized. Studies on isolated frog sciatic nerve preparations have shown that the concentration of tetracaine required to reduce the action potential by 50% is approximately twice the concentration of dibucaine required to produce the same effect (5). Studies utilizing a chronic spinal dog model have recently shown that 0.25% dibucaine and 0.5% tetracaine produce a similar degree and duration of motor blockade in dogs (6). Clinical studies in which dibucaine and tetracaine have been evaluated separately suggest that 0.25% dibucaine and 0.5% tetracaine produce satisfactory sensory analgesia for a variety of surgical procedures with a duration of action of 1 to 3 hours (7). Therefore, the present clinical study was initiated to compare in a double-blind fashion the relative effects of intrathecal dibucaine and tetracaine

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TABLE 1
Comparative Nomenclature of Tetracaine and Dibucaine

Chemical name	Official generic names		Trade name
	U.S.A.	U.K.	
2-(dimethylamino)ethyl-*p*-(butylamino)benzoate monohydrochloride	Tetracaine hydrochloride (U.S.P)	Amethocaine hydrochloride (B.P.)	Pontocaine, Anethaine, Decicain
Hydrochloride of 2-*n*-butoxy-*N*-[2-(diethylamino)ethyl] cinchoninamide monohydrochloride	Dibucaine hydrochloride (N.F.)	Cinchocaine hydrochloride (B.P.)	Nupercaine, Percaine

in man utilizing hyperbaric solutions of 0.25% dibucaine and 0.5% tetracaine.

Patients and Methods

Thirty A.S.A. physical status I and II patients scheduled for orthopedic, urologic, and general surgery of 60 to 90 minutes' duration under spinal anesthesia were included in this study (Table 2).

Following placement of a peripheral intravenous catheter and infusion of approximately 500 ml of lactated Ringer's solution, blood pressure and heart rate were recorded. Dural puncture was performed at the L3-4 interspace using a midline approach with a 26-gauge spinal needle. A volume of 0.5% tetracaine or 0.25% dibucaine in 5.0% glucose believed, on the basis of clinical experience, necessary to achieve a T-6 level of sensory analgesia, was administered. Fifteen patients received an average dose of 11.1 ± 1.6 mg of tetracaine and 15 received an average dose of 5.4 ± 0.7 mg of dibucaine. The study was performed under double-blind, randomized conditions such that neither the patient nor the individual administering the drug and/or evaluating its effect knew which agent was being used.

Twenty-six patients were in the lateral decubitus position and four were sitting during spinal anesthetic administration and all were immediately placed in a horizontal supine position after the injection. The patients who were sitting were not excluded from the study as results in these patients did not differ statistically from those observed in patients in whom injections were made in the lateral position.

Heart rate and blood pressure were measured at 5-minute intervals throughout the anesthetic procedure. Motor blockade and level of sensory analgesia were determined at 2-minute intervals for the first 20 minutes and then every 15 to 30 minutes until signs of sensory spinal anesthesia had regressed to the L-3 dermatomal level. We tried to assign the degree of motor blockade to one of four categories as follows: 0, able to raise straight leg and flex knee and ankle; 1, unable to raise straight leg but able to flex knee and ankle; 2, unable to raise straight leg or flex knee but able to flex ankle; 3, unable to raise straight leg or flex knee or flex ankle. One patient who received tetracaine was unable to move her lower limbs due to joint fusion and was not included in the subsequent motor analyses. Segmental levels of sensory analgesia were tested using response to pinprick in the midclavicular line before and after surgery or in the midaxillary line when the midclavicular was not accessible. Adequacy of spinal anesthesia was judged by the anesthesiologist from the patient's response and the surgical conditions. Patients requiring supplemental analgesia were judged to have an inadequate block.

TABLE 2
Patient Characteristics*

	Dibucaine (n = 15)	Tetracaine (n = 15)
Age (yr)	53.67 ± 19.39	50.77 ± 21.96
Weight (kg)	74.93 ± 17.31	69.0 ± 17.46
Height (cm)	171.67 ± 10.15	169.47 ± 11.28
Dose (mg)	5.43 ± 0.73	11.13 ± 1.64

* Values are means ± SD.

The results were analyzed statistically using nonpaired *t*-test, chi-square test (Yates's correction), and Fisher's exact probability test; $p < 0.05$ was considered statistically significant.

Results

Patients who received dibucaine did not differ significantly from those receiving tetracaine with respect to age, weight, height (Table 2), or numbers in each surgical category (Table 3). There was no difference in mean doses of the two drugs, assuming dibucaine to have twice the potency of tetracaine (Table 2).

TABLE 3

Types of Cases, Adequacy of Block, and Supplementation

Surgical Category	Dibucaine		Tetracaine	
	Inadequate (n = 5)	Adequate (n = 10)	Inadequate (n = 3)	Adequate (n = 12)
Appendectomy		1		
Inguinal herniorraphy			1	1
Cystoscopy		2		2
Transurethral resection of prostate	2*	3	1*	1
Knee arthrotomy	1		1*	3
Leg debridement				1
Below-knee amputation		1		1
Ankle exostosis excision		1		1
Foot amputation/ bunionectomy	1	1		2
Rectal abscess incision and drainage	1*	1		
Mean time from injection to completion of surgery (min ± SD)	93.2 ±46.0	60.9 ±32.0	72.0 ±21.1	91.2 ±28.1

* General anesthesia.

Times for onset and regression of anesthesia to levels T-10 and T-12 were the same for both agents (Table 4). The segmental levels of analgesia in the two groups at each time interval were not significantly different (Fig 1). Five of 15 patients given dibucaine received supplemental analgesia, three with general anesthesia and two with intravenous fentanyl up to 0.1 mg. Three of 15 patients who received tetracaine required supplemental analgesia, two with general anesthesia and one with fentanyl and 50% nitrous oxide in oxygen. The difference between the two groups was not statistically significant (Table 3). The mean times from spinal injection to completion of surgery are also given in Table 3. There was no statistically significant difference between these times when patients with inadequate blocks were compared with patients with adequate blocks within the two drug groups.

Significant differences existed between the two groups when motor function was compared. Complete motor blockade (3) was achieved more frequently in patients given tetracaine (71%) than in those given dibucaine (27%) ($p < 0.05$). However, the frequencies for one and two blocks were no different (Table 5).

The major complication encountered during spinal anesthesia was hypotension. One patient given dibucaine and two patients given tetracaine were treated with phenylephrine infusions. No rigid criteria were laid down for the definition or treatment of hypotension. These were left to the judgment of the attending anesthesiologists. Excluding these three patients, the percentage decrease in mean arterial pressure during the first 90 minutes after spinal injection was significantly greater in patients who had received tetracaine Fig 2). This difference was particularly marked 10 minutes after injection ($p < 0.001$).

The incidence of bradycardia was unremarkable. Atropine was used to treat one patient given dibucaine

TABLE 4

Onset and Duration of Sensory Analgesia*

	Dibucaine (n = 15)	Tetracaine (n = 15)
	min	
Onset to:		
T 12	2.57 ± 0.96	2.80 ± 1.66
T 10	4.82 ± 1.59	4.83 ± 2.27
Regression to:		
T 10	103.07 ± 40.61	97.40 ± 37.25
T 12	156.29 ± 47.27	136.47 ± 36.60

* Values are Means ± SD.

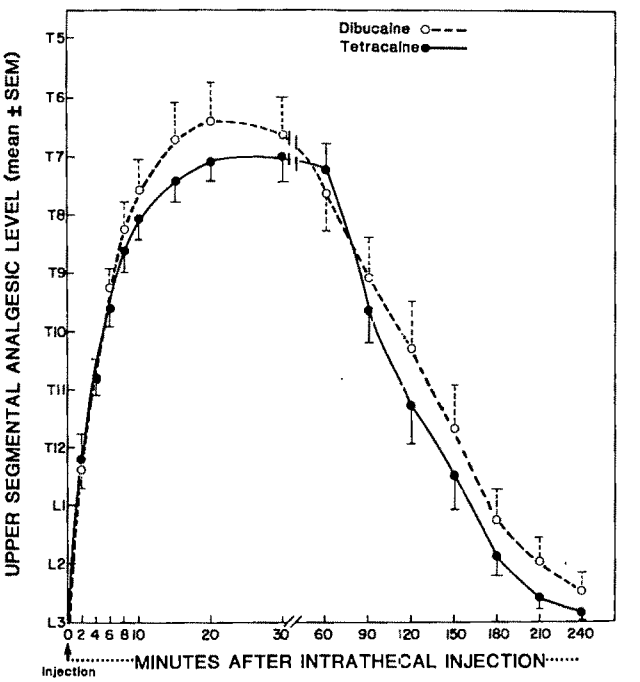


FIG 1. Upper dermatomal segmental analgesic level (mean ± SEM) following intrathecal administration (arrow) of dibucaine (dashed line) or tetracaine (solid line).

TABLE 5

Degree of Motor Blockade

Category of motor function	Dibucaine (n = 15)	Tetracaine (n = 14)
1	14	14
2	10	13
3	4	10*

* $p < 0.05$.

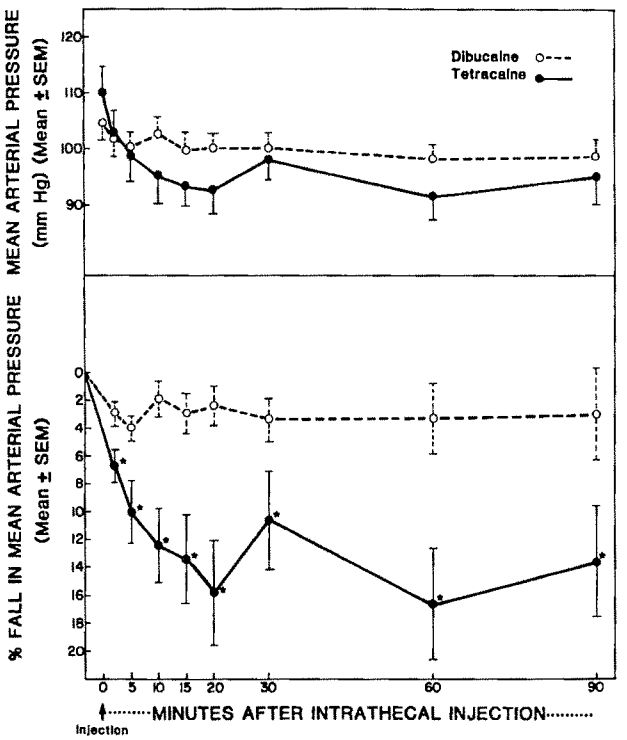


FIG 2. Arterial blood pressure (upper curves) and percent change in mean blood pressure from control value (lower curves) following intrathecal administration (arrow) of dibucaine (dashed line) or tetracaine (solid line). Values are means ± SEM. * p = 0.01 to 0.001.

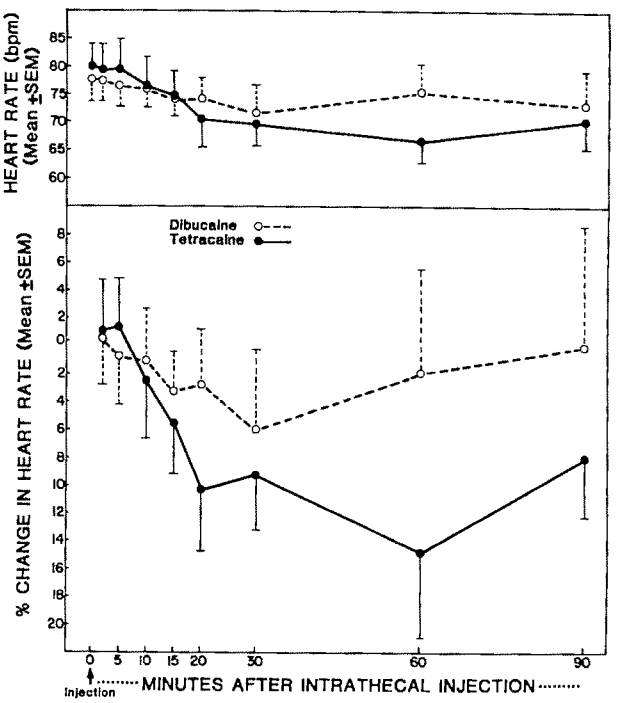


FIG 3. Heart rate (upper curves) and percent change in heart rate (lower curves) following intrathecal administration (arrow) of dibucaine (dashed line) or tetracaine (solid line). Values are means ± SEM.

who was subject to vasovagal attacks. Excluding this patient, tetracaine produced a greater percent decrease in heart rate than dibucaine but the difference was not statistically significant (Fig 3).

Discussion

Dibucaine and tetracaine have been used clinically for approximately 50 years as spinal anesthetic agents of high potency and moderately long duration of action. There are differences in names, use, and availability of the two drugs in various parts of the world. Whether differences also exist regarding their comparative anesthetic characteristics has not been well established despite their long-term clinical use. On the basis of isolated nerve studies (5), intact animal studies (6), and general clinical experience (7) dibucaine is believed to be approximately twice as potent as tetracaine. The present study indeed demonstrates little difference in onset, spread, and duration of sensory analgesia between hyperbaric solutions of 0.25% dibucaine and 0.5% tetracaine. Tetracaine produced more profound motor blockade and more extensive sympathetic blockade as indicated by the greater degree of motor impairment and hypotension in the patients given tetracaine. These results suggest that dibucaine may be twice as potent as tetracaine for blocking of sensory fibers but not for sympathetic or motor fibers.

Supplemental analgesia was required in 20% of the patients given tetracaine and in 33% of those given dibucaine despite an average T-7 level of sensory analgesia to pinprick with both drugs. Two patients requiring general anesthesia were psychologically unsuited for spinal anesthesia so these two failures could be attributed in part to faulty patient selection. At least one failure is attributable to faulty technique. The remaining five patients required supplemental analgesia due to inadequate spinal anesthesia from the start. These results suggest that a larger dose of both agents is required to provide adequate surgical anesthesia for most patients. The fear of exaggerated spread of spinal anesthesia following use of large doses of intrathecally administered local anesthetic agents is not substantiated by the study of Brown et al (8) who failed to observe any difference in the spread of sensory analgesia following the use of 10 or 15 mg of hyperbaric tetracaine in the supine position.

REFERENCES

1. Howard Jones W. Spinal analgesia—a new method and a new drug—percaine. Br J Anesth 1930;7:99-113; 7:146-56.
2. Silverton RJ. Spinal analgesia: the percaine-ephedrine technique. Aust NZ J Surg 1934;3:223-34.

3. Sise LF. Pontocain—glucose solution for spinal anesthesia. Surg Clin North Am 1935;15:1501–11.
4. Roman DA, Adriani J. Nupercaine-glucose for spinal anesthesia; results of over 5000 clinical administrations. Anesthesiology 1949;10:270–79.
5. Truant AP, Takman B. Differential physical-chemical and neuropharmacologic properties of local anesthetic agents. Anesth Analg 1959;38:478–84.
6. Feldman HS, Covino BG. A chronic model for investigation of experimental spinal anesthesia in the dog. Anesthesiology 1981;54:148–52.
7. Lund PC. Principles and practice of spinal anesthesia. Springfield, IL: Charles C Thomas, 1971:198.
8. Brown DT, Wildsmith JAW, Covino BG, Scott DB. Effect of baricity on spinal anaesthesia with amethocaine. Br J Anaesth 1980;52:589–96.

Cryoanalgesia for Relief of Pain after Thoracotomy

One hundred patients undergoing thoracotomy had their intercostal nerves blocked by cryoanalgesia before closure, and the effect of this treatment on postoperative pain was evaluated. The intercostal nerve at the thoracotomy space and two intercostal nerves above and two below the space were frozen for 30 seconds. The probe was allowed to defrost in situ to facilitate its removal. Each nerve was refrozen at the same site for a further 30 seconds in a similar manner. Of the 100 patients, 79 were free of pain, 12 had some discomfort, and nine reported severe pain necessitating narcotic analgesia (mean 1.5 injections per patient). Overall, lack of pain and greater alertness much enhanced the value of physiotherapy, which resulted in a low incidence of complications and a smooth recovery. The technique of cryoanalgesia is simple, extremely effective, and apparently offers benefits not conferred by other methods of preventing pain after thoracotomy. (*Maiwand O, Makey AR: Cryoanalgesia for relief of pain after thoracotomy. Br Med J 1981;282:1749–50*)

technical COMMUNICATIONS

A Simple Flueric High Frequency Jet Ventilator

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Fluidics is the technology of using fluids (gases or liquids) to sense, power, or control. It is composed primarily of two major areas: pneumatics (fluidics with moving parts) and fluerics (fluidics without moving parts) (1, 2). In high frequency jet ventilation (HFJV), the control of gas stream pulsation is most commonly accomplished with electronically controlled solenoid valves (3, 4). Pneumatic techniques utilizing multicomponent flueric control of mechanical valves have also been reported (5). This paper describes the design of a simple high frequency jet ventilator controlled by a single flueric component (bistable amplifier-oscillator) located in the power jet gas stream and its application in the respiratory support of two pediatric patients with terminal pulmonary disease.

System Description and Operation

A schematic diagram of this simple flueric high frequency jet ventilator is shown in Fig 1. The ventilator consists of a flueric oscillator with two identical feedback control circuits consisting of a capacitor and a needle value (Figs 1 and 2). Two exhaust lines exit from the oscillator (Fig 1). One is connected to the jet catheter located in the endotracheal tube (Fig 3). The other exhausts directly to the atmosphere. The supply gas (oxygen/nitrogen) flows to the oscillator through a rotameter and is controlled by an inline pressure regulator. Either pressure gauges or transducers located in the supply and exhaust lines are used to monitor operational pressures and conditions.

The main component of the ventilator consists of a single bistable flueric amplifier which functions as an oscillator because of the addition of a feedback control circuit between each exhaust port and the corresponding ipsilateral amplifier control port (Fig 2). A supply gas stream flowing through the oscillator input jet tends to enter preferentially and adhere to the wall of one, of two exhaust ports (Coanda effect: A fluid jet flowing close to a surface tends to be deflected toward the surface and attaches to it because of the inability of the jet to entrain fluid from the side adjacent to the surface.) (Fig 2). Each exhaust port has a feedback circuit consisting of a capacitor (bottle) in series with a variable resistor (needle valve). Gas continues to flow through this port until the pressure in the ipsilateral feedback control port exceeds the pressure in the contralateral feedback control port. The resultant pressure imbalance causes the input jet stream to switch to the opposite exhaust port. Flow continues in this direction until another feedback control pressure imbalance again switches the stream

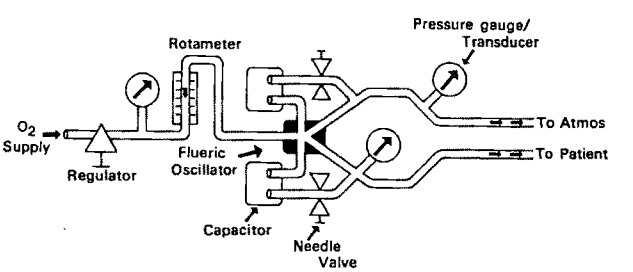


FIG 1. Schematic diagram of flueric high frequency jet ventilator system. Key components consist of flueric amplifier functioning as oscillator because of addition of two feedback control circuits consisting of capacitor (bottle) and resistor (needle valve) in series between each exhaust and control port.

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Received from the Departments of Anesthesiology and Pediatrics, University of Arizona Health Sciences Center, Tucson, Arizona. Accepted for publication September 29, 1981.
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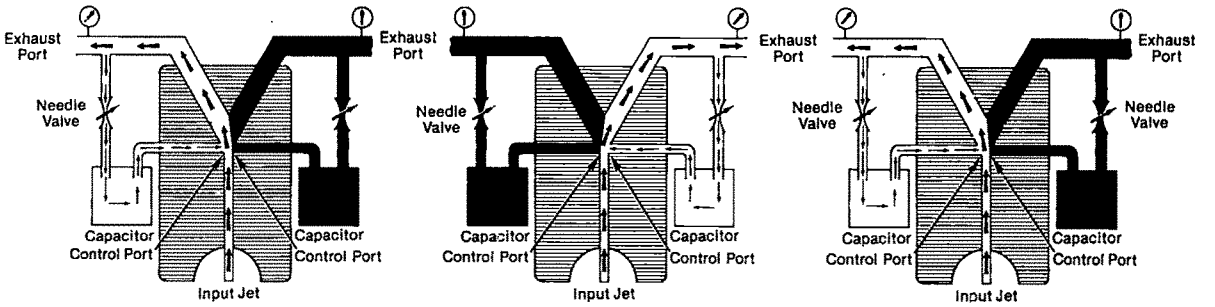


FIG 2. Schematic diagram depicting oscillator operation cycle. Oscillations are produced by pressure imbalance between feedback control ports. Darkened areas indicate no gas flow.

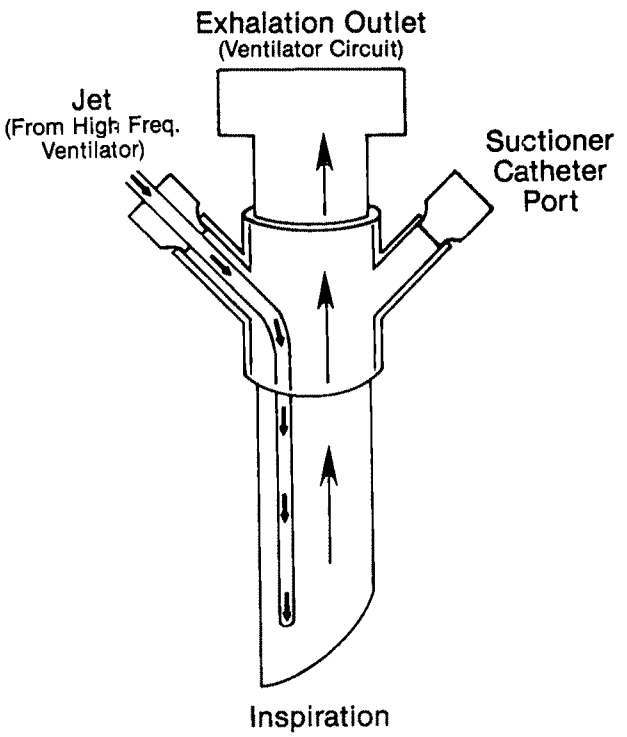


FIG 3. Schematic diagram of endotracheal tube with jet catheter. Jet was introduced through endotracheal tube wall and supported with external plastic sleeve.

back to the first exhaust port. Oscillator switching frequencies depend upon supply gas flow and pressure as well as resistance and capacitance characteristics of the feedback control pressure loops. For a given inlet gas flow, frequencies are changed by adjusting both needle valves.

Either one or both of the pulsed outputs may be used for HFJV. In the cases to be described, one oscillator exhaust vented to the atmosphere while the other was connected to a jet that consisted of a plastic intravenous catheter introduced through a hole cut into the wall of the endotracheal tube (Fig 3). A second hole was cut on the opposite side of the endotracheal tube to allow for the introduction of a suction catheter. A plastic sleeve adapter was designed to provide support and ease of removing both jet and suction catheters (Fig 3). This particular design enabled sterile removal and reinsertion of the jet during the period of tracheal care.

A pressure transducer (PT-22 Pi-Tran), or a Dwyer Series 2000 Magnehelic 10 psi pressure gauge, or both were connected into the exhaust gas streams (Fig 1). The transducer was connected to a Hewlett-Packard model 5302A counter and a Tektronix model T912 oscilloscope. Volumetric flow rates were estimated by use of a Gilmot rotameter placed in the gas supply line to the flueric oscillator. The oxygen supply was mixed with air through a Bird Corporation oxygen blender. The patient gas stream was humidified with a modified De Vilbiss ultrasonic nebulizer.

Using inlet gas pressures ranging from 25 to 40 psi, total flow through the oscillator varied from 8 to 20 L/min resulting in minute volumes through one exhaust port of 4 to 10 L. Depending on resistance and capacitance in both feedback and patient circuits, maximum peak airway pressures of 10 cm H_2O were measured in the circuit at the outlet of the endotracheal tube. Frequencies ranged from 120 to 500 min^{-1}. The flueric system was used simultaneously with a Bourns Life Systems Infant Volume-Cycled Ventilator (model LS104-150) which provided continuous positive airway pressure (CPAP) or positive end-expired pressure (PEEP) control and occasional sighs. This was accomplished by simply leaving the endotracheal tube attached to the patient circuit of the Bourns system via conventional adaptors (Fig 3).

Clinical Application and Results

In the following two clinical situations, with approval of the Human Subjects Committee including the Division of Biomedical Engineering and parental consent, HFJV with this flueric oscillator system was utilized.

Case Reports

Case 1

A 1200-gm boy was the first-born twin by cesarean section to a 28-year-old gravida 1, para 0 at 26 weeks of gestation. The neonate was initially pink and vigorous with Apgar scores of 7 and 5. However, his condition soon deteriorated and required ventilator support as respiratory distress syndrome (RDS) ensued. While ventilated with a Bourns Infant Volume Ventilator, the infant required increasing airway pressures and oxygen concentrations (F_{IO_2}). Emphysematous blebs and numerous pneumothoraces required chest tubes. At age 6 weeks, worsening gas exchange, compliance, and barotrauma had necessitated small tidal volumes (28 ml), and rapid rate (80 min^{-1}) with continuous positive airway pressure (3 cm H_2O) (Table). Peak airway pressures of 70 cm H_2O and a F_{IO_2} of 1.0 were required to maintain an arterial P_{O_2} of 43 torr.

HFJV via the fluidic oscillator was introduced via a 14-gauge catheter (2.1-mm diameter) passed through a hole in the sidewall to the distal tip of a 4-mm i.d. endotracheal tube. For suctioning, the HFJV catheter was withdrawn. The child was gradually weaned from the Bourns to the flueric system by decreasing tidal volume and rate of the Bourns while simultaneously increasing frequency and flow of the flueric system. Complete support with HFJV was implemented on day 33 of HFJV with a frequency of 430 min^{-1} and was associated with increased Pa_{O_2} (59.5 torr) and reductions in airway pressure (10 cm H_2O), F_{IO_2} (0.6), and Pa_{CO_2} (62.1 torr). Pa_{CO_2} values ranging from 50 to 60 torr and a slow weaning process which continued for 33 days were arbitrarily chosen by the neonatologists.

Optimal arterial blood gas tensions were associated with a rocking chest motion and a specific auscultatory sound pitch determined with use of a differential stethoscope. Chest tube air leakage, radiographic bleb size, and interstitial air were also diminished and chest tubes were removed. HFJV frequencies were adjusted between 150 and 430 min^{-1}. Independent of Pa_{CO_2}, the infant breathed spontaneously when HFJV frequencies exceeded 250 min^{-1}, but was apneic at lower rates. Higher HFJV rates appeared necessary as the child's disease progressed and his compliance worsened. He died due to sepsis and cardiac and renal failure during the 6th week of HFJV support.

Case 2

A 4-month old boy had been healthy prior to 6 weeks of nonproductive cough, fevers of 39 C, and 2 weeks of tachypnea and irritability. Pulmonary coccidiomycosis was diagnosed, and the patient was given intravenous amphotericin. His pulmonary function worsened over several weeks resulting in decreased arterial oxygen and increased carbon dioxide tensions despite intubation and respiratory support with the Bourns Infant Volume Ventilator. Chest x-rays indicated necrotizing pneumonia. Because the child was requiring higher ventilator rates (80 min^{-1}) with the Bourns to maintain gas exchange and minimize barotrauma, the flueric HFJV system was used in a manner similar to that used in case 1. During weaning, bilateral pneumothoraces developed and chest tubes were required. With HFJV some improvement in Pa_{CO_2} was observed (Table). After several hours, the patient succumbed to his underlying disease.

Discussion

Applications of fluidics to ventilator design are well known. The majority of these applications are pneumatic as they use moving parts in some portion of the operational cycle. The fluidic components are typically used only for control. True flueric ventilators are rare: only one major type (Army's Emergency Ventilator with variations) has been successfully utilized (2).

Fluidic (pneumatic) devices have been successfully utilized for HFJV. Klain and Smith (5) described a pneumatic unit using four flueric amplifiers with a

TABLE

Arterial Blood Gas Tensions*

Time	HFJV rate	Bourns rate	TV	CPAP	Arterial blood gas tensions		
					F_{IO_2}	P_{O_2}	P_{CO_2}
	cpm		*ml*	*cm H_2O*		*torr*	
Case 1							
0	—	80	28	3	1.0	42.7	86.5
1 day	165	20	20	3	0.9	59.8	73.5
33 days	480	—	—	—	0.6	69.5	62.1
Case 2							
0	—	80	75	6	1.0	42.0	39.7
6 hr	225	5	65	6	1.0	66.0	49.0
8 hr	100	5	65	6	1.0	94.3	47.0
12 hr	420	—	—	—	—	tcO_2†	

* Abbreviations used are: HFJV, high frequency jet ventilation; TV, total ventilation; CPAP, continuous positive airway pressure.
† Transcutaneous oxygen (tcO_2) 75 ± 5.

logic circuit for control of a mechanical interfacing spool valve which interrupts the jet supply source at the appropriate times. In contrast to the Klain-Smith unit, the device described in this paper uses a single flueric oscillator without moving parts.

During the present use, one exhaust stream was vented directly into the atmosphere allowing for effective operation but inefficient supply gas utilization. The nonpatient stream can be partially clamped with proper feedback to conserve the quantity of supply gas utilized or used in concert with the original patient stream for endobronchial high frequency alternating lung ventilation (6).

Potential advantages of a pure flueric device include simplicity, ease of operation, reliability, and low cost. The device described operated continuously for approximately 7 weeks without malfunction. Nurses and residents became comfortable and efficient in its use and operation. Although the patients succumbed to their disease processes, the flueric system demonstrated clinical capabilities.

ACKNOWLEDGMENTS

The authors would like to acknowledge the assistance given to them by the intensive care unit nursing staff and anesthesiology and pediatrics residents; particularly Drs. Earl Leeman and Mike Humphrey. The authors also want to thank Christian Pickering and Carole Wiseman for their assistance in preparing the manuscript, and the University of Arizona Engineering Affiliates Program for technical and financial support.

REFERENCES

1. What you should know about fluidics. Technical manual. Thiensville, WI: National Fluid Power Association, 1972.
2. Mushin WW, Rendell-Baker L, Thompson PW, Mapleson WW. Historical background to automatic ventilation. In: Automatic ventilation of the lungs. 3rd ed. London: Blackwell Scientific Publications, 1980:223.
3. Sjöstrand U. Review of the physiologic rationale for the development of high frequency positive pressure ventilation—HFPPV. Acta Anaesthesiol Scand Suppl 1977;64:7–27.
4. Carlson GC, Miodownik S, Ray C, Kahn RC. Technical aspects and clinical implications of high frequency jet ventilation with a solenoid valve. Crit Care Med 1981;9:47–50.
5. Klain M, Smith RB. Fluidic technology. Anaesthesia 1976;31: 750–7.
6. Hameroff SR, Calkins JM, Waterson CK, Kanel JS. High frequency alternating lung ventilation. Anesthesiology 1981;54: 237–9.

Predicting Survival from Out-of-Hospital Cardiac Arrest

A scoring system was developed to predict survival following out-of-hospital cardiac arrest. The score is calculated from four pieces of information readily obtainable by emergency personnel directly at the scene of the arrest. The four items, known as the ACLS score, are: A, arrest witnessed; C, cardiac rhythm; L, lay bystander cardiopulmonary resuscitation (CPR); S, speed (response time of paramedic unit). Among 22 patients with favorable findings on all four predictive variables (witnessed arrest, ventricular fibrillation, bystander CPR, paramedic response time less than 4 minutes), 15 (70%) were discharged alive. The ACLS score for this group of patients was 70%. Among 97 patients with the most unfavorable findings (ACLS score was 0), one (1%) was discharged. The authors believe the score can provide emergency personnel with a realistic appraisal of the likelihood of successful resuscitation. (*Eisenberg M, Hallstrom A, Bernger L: The ACLS score: predicting survival from out-of-hospital cardiac arrest. JAMA 1981;246:50–2*)

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Enflurane and Isoflurane Stimulate Calcium Transport by Cardiac Sarcoplasmic Reticulum

Thomas J. J. Blanck, MD, PhD,* and Meff Thompson, AB†

The cardiac sarcoplasmic reticulum (SR) controls myoplasmic Ca^{2+} availability and can modulate the inotropic state of the myocardial cell (1). It has been demonstrated that the volatile anesthetics, halothane, enflurane, and isoflurane, depress cardiac contractility (2–4). The sarcoplasmic reticulum is one possible site at which these anesthetics act to alter contractility as the SR (*a*) controls calcium availability, and (*b*) is a membranous system in which the lipophilic volatile anesthetics accumulate (5).

Our recent report (6) has demonstrated that halothane can either stimulate or inhibit SR calcium uptake. These effects were related to the concentration of adenosine triphosphate (ATP), the substrate and energy source for the transport of calcium. At low ATP concentrations halothane in increasing concentrations first stimulated and then inhibited Ca^{2+} uptake; at higher ATP concentrations halothane only inhibited calcium uptake. In this paper we describe some similar effects of enflurane and isoflurane on SR calcium uptake, and the possible common mechanism of action of these volatile anesthetics.

Methods and Materials

Cardiac SR was prepared as previously described by a modification of the method of Harigaya and Schwartz (6, 7). All reactions containing volatile anesthetics were performed in 31.6 ml vials with Teflon caps. Anesthetic was added in liquid form with a Hamilton microliter syringe and the anesthetic vapor concentration measured by infrared spectroscopy (8).

Calcium uptake into the SR was measured by a modification of the Millipore filtration technique using glass fiber filters (9). Reactions were performed in 1 ml of total volume at pH 7.3, 37 C, for 2 minutes. All reactions contained 5 mM $MgCl_2$, 5 mM sodium azide, 5 mM potassium oxalate, 0.1 mM ethylene glycol bis (beta-aminoethyl ether)-*N,N,N',N'*-tetraacetic acid (EGTA), 0.1 mM $CaCl_2$, 100 mM KCl, and 50 mM 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (Hepes). The reaction was initiated by the addition of ATP. Protein concentration was measured by the Coomassie binding method using serum albumin as standard (10).

Hepes was purchased from Calbiochem-Behring Corp., American Hoechst Corp. GFF glass fiber filters were purchased from Whatman, Inc. ^{45}Ca, 10 mCi/ml, was purchased from New England Nuclear Co. Liquid scintillation counting was performed in a Packard Prias counter using Cytoscint scintillation fluid purchased from West Chemical Co.

Results

ATP and Anesthetic Dependence of Calcium Uptake

The ATP concentration dependence of calcium uptake was examined at several concentrations of enflurane and isoflurane (Figs 1 and 2). In the absence of anesthetic, full saturation of the calcium transport enzyme occurred at approximately 5 mM ATP. Enflurane at 0% to 2.82% stimulated the rate of calcium uptake (Fig 1) and decreased the concentration of ATP required for saturation of the transport enzyme. Similar effects were observed with 0% to 1.99% isoflurane (Fig 2). The stimulatory effect of both anesthetics was most obvious at low ATP concentrations (<3 mM); this is most easily observed in Fig 3 where the data from Figs 1 and 2 are expressed as a function of anesthetic concentration. At high ATP concentrations (5 and 10 mM), isoflurane either had no effect or inhibited the rate of calcium uptake; this is similar to our observations with halothane (6). We have also previously reported that enflurane at high concentrations (~5%) and at 5 mM ATP inhibited calcium uptake (11). Apparently all three anesthetics have two separate effects: (*a*) to stimulate calcium uptake at low ATP concentration; and (*b*) to inhibit calcium uptake at high ATP concentration.

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Supported by grant 2R01 GM25180-04 from the National Institutes of Health and the Muscular Dystrophy Association.

Received from the Departments of Anesthesiology and Pharmacology, University of Arizona Health Sciences Center, Tucson, Arizona. Accepted for publication October 12, 1981.

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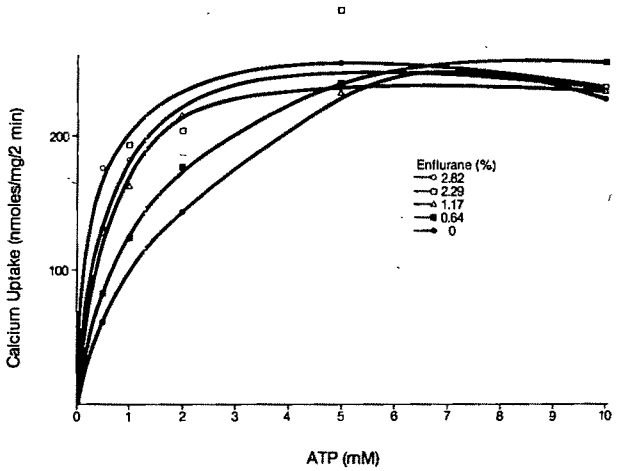


FIG 1. ATP dependence of calcium uptake by sarcoplasmic reticulum (SR) effect of enflurane. Experiment performed at 37 C, pH 7.3 with 100 μg/ml of SR protein. Enflurane was present in concentrations of: 0% (●), 0.64% (■), 1.17%; (△), 2.29% (□), and 2.82% (○).

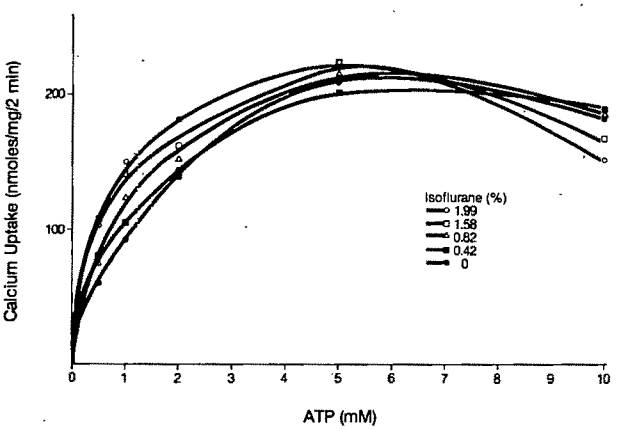


FIG 2. ATP dependence of calcium uptake by SR effect of isoflurane. Experiment performed as described in Fig 1. Isoflurane was present in concentrations of 0% (●), 0.42% (■), 0.82% (△), 1.58% (□), and 1.99% (○).

The data of Figs 1 and 2 were subjected to weighted nonlinear regression analysis to obtain statistical estimates of the kinetic parameters K_m and V_{max} of the Michaelis-Menten equation (12). Data obtained at 10 mM ATP were deleted from this analysis as 10 mM ATP alone inhibited the rate of calcium uptake and probably involved a different mechanism. The results are shown in Fig 4. Both enflurane and isoflurane markedly decrease K_m with a smaller effect on V_{max}. The decrease in K_m is nonlinear response to anesthetic concentration; approximately 70% of the decrease in K_m has occurred at 1% concentrations of both enflurane and isoflurane.

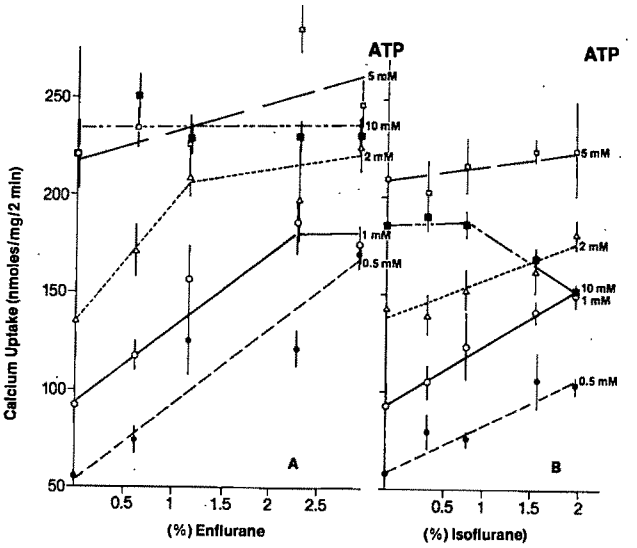


FIG 3. Anesthetic dependence of calcium uptake at varying ATP concentrations. A, Enflurane (same data as in Fig 1); B, isoflurane (same data as in Fig 2). Each point is mean of four experimental determinations; bars indicate standard deviations of mean.

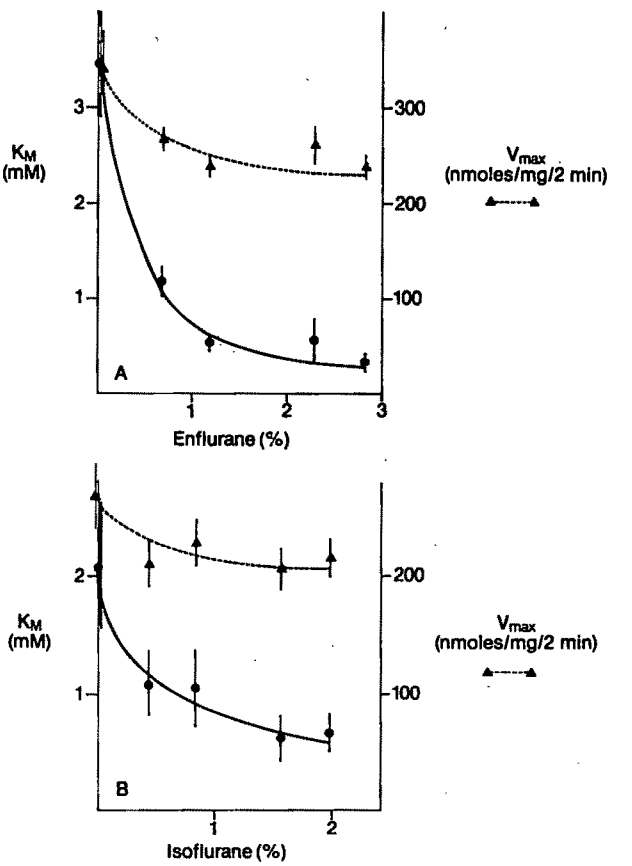


FIG 4. Anesthetic dependence of K_m (●) and V_{max} (▲) as determined by weighted nonlinear regression analysis of data in Figs 1 and 2 (12). A, Enflurane; B, isoflurane. Each point is derived from 16 experimental observations; bars indicate standard error of estimates.

Discussion

The volatile anesthetics, halothane, enflurane, and isoflurane, are halogenated hydrocarbons that have similar pharmacologic properties. They cause anesthesia and decrease the contractile activity of the heart. The mechanism of both these effects is unknown. We have undertaken an investigation of one possible aspect of the anesthetic depression of the myocardium because of: (*a*) its obvious clinical importance; and (*b*) in order to study molecular effects of the anesthetics in a system that has been well defined. This study and our previous paper (6) have demonstrated that the three anesthetics, halothane, enflurane and isoflurane, all act to stimulate calcium uptake by the cardiac sarcoplasmic reticulum in vitro. The stimulatory effect occurs at low ATP concentrations and at clinically relevant anesthetic concentrations. All three anesthetics decrease the K_m for ATP of the Ca^{2+}, Mg^{2+} ATPase, the enzyme in the sarcoplasmic reticular membrane responsible for calcium transport. The data suggest that the volatile anesthetics increase the affinity of the enzyme for ATP, i.e., the substrate binding sites on the enzyme are saturated at a lower concentration of ATP. The rate of uptake is not stimulated beyond the maximal velocity, V_{max}, of the enzyme, suggesting that the effects of the three anesthetics are to improve ATP availability to the transport system but not to alter the intrinsic catalytic properties of the enzyme. One might assume that stimulation of Ca^{2+} transport by volatile anesthetics does not occur at higher ATP concentrations because the enzyme is already working at its maximal capacity and has a ready supply of ATP such that enhancement in availability of ATP will not improve the reaction rate.

We have noted previously that halothane inhibits calcium uptake when the concentration of ATP is 5 mM or higher and the halothane concentration is greater than 1%. We have previously observed that the enzyme activity is decreased by high concentrations of enflurane at 5 mM ATP (11) and now demonstrate that isoflurane at 1% or more decreases Ca^{2+} uptake and decreases V_{max}. It appears that the effects of halothane, isoflurane, and enflurane are similar, differing only in their concentration range. At this time our data are not sufficient to determine whether two separate mechanisms are involved in stimulation and inhibition, although this would seem most probable. The data suggest that at low anesthetic concentration the binding of ATP is facilitated either by increase in affinity or by greater exposure of the binding site. At higher anesthetic concentrations at which we see inhibition of Ca^{2+} uptake, some step in the catalytic sequence other than ATP binding might be altered. The inhibitory effects, like the stimulatory effects, cannot yet be assigned to a direct action of anesthetic on either the enzyme or the phospholipid membrane which surrounds the enzyme.

All three anesthetics at clinically relevant concentrations stimulate Ca^{2+} transport. In the range of ATP that appears to pertain in vivo (5 mM) the volatile anesthetics, enflurane, isoflurane, halothane, appear to have little apparent effect on the calcium uptake process. However, as we have previously stated, if ATP declines as in an ischemic heart or in the heart exposed to ischemic cold arrest during cardiopulmonary bypass, the availability of Ca^{2+} for contractile elements might be decreased by the presence of the volatile anesthetics. Thus far no clinical or experimental evidence is available to support this hypothesis. In the normal heart in which the volatile anesthetics depress contractility, sites other than the SR are probably also involved (13). Anesthetics are concentrated in membranous and hydrophobic environments in cells. Clinical concentrations of anesthetics in the blood and tissues are approximately 1 mM (14), and it seems unlikely that at these high concentrations any single site in the myocardial cell will be *the* site at which the volatile anesthetics act. It is our expectation that the volatile anesthetics will be found to have many small but significant effects at several sites in the excitation-contraction mechanism that result in depression of contractility.

REFERENCES

1. Katz AM. Physiology of the heart. New York: Raven Press, 1977.
2. Calverley RK, Smith NT, Prys-Roberts C, Eger EI, Jones CW. Cardiovascular effects of enflurane anesthesia during controlled ventilation in man. Anesth Analg 1978;57:619–28.
3. Horan BF, Prys-Roberts C, Hamilton WK, Roberts JG. Hemodynamic responses to enflurane anesthesia and hypovolaemia in the dog and their modification by propranolol. Br J Anaesth 1977;48:1189–97.
4. Horan BF, Prys-Roberts C, Roberts JG, Bennet MJ, Foex P. Hemodynamic responses to isoflurane anaesthesia and hypovolaemia in the dog and their modification by propranolol. Br. J Anaesth 1977;49:1179–87.
5. Mastrangelo CJ, Trudell JR, Edmunds HN, Cohen EN. Effect of clinical concentrations of halothane on phospholipid membrane fluidity. Mol. Pharmacol 1978;14:463–7.
6. Blanck TJJ, Thompson M. Calcium transport by cardiac sarcoplasmic reticulum: modulation of halothane action by substrate concentration and pH. Anesth Analg 1981;60:390–4.
7. Harigaya S, Schwartz A. Rate of calcium binding and uptake in normal animal and failing human cardiac muscle. Circ Res 1969;25:781–94.
8. Blanck TJJ. A simple closed system for performing biochemical experiments at clinical concentrations of volatile anesthetics. Anesth Analg 1981;60:435–6.

9. Martonosi A, Ferretos R. Sarcoplasmic reticulum. I. The uptake of Ca^{2+} by sarcoplasmic reticulum fragments. J Biol Chem 1964;239:648–58.
10. Bradford MM. A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. Anal Biochem 1976;72:248–54.
11. Conahan TJ, Blanck TJJ. Sarcoplasmic reticulum: enflurane effect on Ca^{2+} dynamics. Anesthesiology 1979;51:5146.
12. Wilkinson GN. Statistical estimates in enzyme kinetics. Biochem J 1961;80:324–32.
13. Pask HT, England PJ, Prys-Roberts C. Effects of volatile inhalational anesthetic agents on isolated bovine cardiac myofibrillar ATPase. J Mol Cell Cardiol 1981;13:293–301.
14. Larson CP, Eger EI, Severinghaus JW. The solubility of halothane in blood and tissue homogenates. Anesthesiology 1962;23:349–55.

Transcutaneous P_{O_2} Monitoring during Pediatric Surgery

The value of continuous transcutaneous oxygen (P_{O_2}) monitoring in the presence of halothane and nitrous oxide (N_2O) was studied in 10 infants. All infants were continuously monitored during the study with a Clark-type skin electrode with a Mylar membrane. The polarization voltage of the membrane was changed to 600 mV to make it insensitive to N_2O and halothane. The accuracy of transcutaneous P_{O_2} was compared with simultaneously measured Pa_{O_2} at different intervals. Correlation of Pa_{O_2} with transcutaneous P_{O_2} was sought during an hypoxic-normoxic state (Pa_{O_2} between 27 and 92 torr) and an hyperoxic state (Pa_{O_2} between 105 and 439 torr). During the hypoxic-normoxic state, the correlation between Pa_{O_2} and transcutaneous P_{O_2} values was 0.94. During the hyperoxic state, poor correlation existed between Pa_{O_2} and transcutaneous P_{O_2} ($r = 0.51$). Although transcutaneous P_{O_2} did not correlate with Pa_{O_2} during hyperoxia, it consistently overestimated Pa_{O_2} and thereby, provided a predictive ability by over-diagnosing hyperoxia. When combined with continuous monitoring of inspired oxygen tension to maintain normoxia, continuous monitoring of transcutaneous P_{O_2} will reduce the frequency of Pa_{O_2} analysis and improve patient care during anesthesia. (*Venus B, Patel KC, Pratap KS, Konchigeri H, Vidyasagar D: Transcutaneous PO_2 monitoring during pediatric surgery. Crit Care Med 1981;9:714–6*)

CLINICAL reports

Pneumoperitoneum and Cardiac Arrest during Craniofacial Reconstruction

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One-stage craniofacial reconstructions are performed in many centers for cosmetic correction of such craniofacial dysostoses of Crouzon's syndrome, Apert's syndrome, and hypertelorism with craniosynostosis (1, 2). The anesthetic management and intraoperative care of patients undergoing lengthy craniofacial reconstructions have recently been reviewed (1, 2). Finucane et al (2) reported a mean operative duration of 14.2 hours and a mean blood loss of 6.06 ml/kg/hr during a series of 14 craniofacial reconstructions in children (2). Major emphasis has been placed on humidification of inspired gases during these lengthy procedures, estimation and management of massive blood loss, regulation of body temperature, and therapeutic management of cerebral edema using deliberate mechanical hyperventilation, intravenous steroids and diuretics, and occasionally continuous drainage of cerebrospinal fluid from the subarachnoid space (1, 2). Preoperative airway assessment is also necessary, particularly if early tracheostomy is indicated for intraoperative airway maintenance during major facial osteotomies.

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Received from the Department of Anesthesiology, Ochsner Medical Institutions, 1516 Jefferson Highway, New Orleans, Louisiana 70121. Accepted for publication September 25, 1981.

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Recent tracheostomy followed by prolonged mechanical ventilation in children, as during craniofacial reconstruction, may be associated with significant extrapleural air leaks in spite of low mean airway pressures (3, 4). Subcutaneous and mediastinal emphysema are relatively common and usually benign indicators of air leaks following tracheostomy in children (4, 5). Pneumothorax, on the other hand, occurs less frequently and can produce fatal tension pneumothorax if unrecognized during mechanical ventilation (6). Pneumoperitoneum and pneumopericardium following tracheostomy are the least frequently reported complications of extrapleural air leaks (3, 4, 7). We report a case of massive pneumoperitoneum with cardiac arrest in a 2-year-old child during craniofacial reconstruction occurring after 12 hours of mechanical ventilation and more than 24 hours after elective preoperative tracheostomy.

Case Report

A 2-year-old, 16-kg girl with congenital hypertelorism and multiple-suture craniosynostosis underwent tracheostomy the day before scheduled craniofacial reconstruction. The tracheostomy was performed under general endotracheal anesthesia without complications. A postoperative chest roentgenogram was not obtained.

On the morning of craniofacial reconstruction, the child was premedicated with morphine sulfate, 2.5 mg, hydroxyzine, 35 mg, and atropine, 0.3 mg, intramuscularly. General anesthesia was induced with 60% N_2O in O_2 and halothane administered through the tracheostomy. Following induction, the 4.0-mm i.d. metal tracheostomy cannula was removed and replaced with a 5.0-mm i.d. cuffed armored tracheal tube. After determining that breath sounds were clear and equal bilaterally, the tracheal tube was sutured in place, and controlled mechanical hyperventilation was instituted with an Ohio pediatric volume ventilator. Pancuronium, 2.0 mg, was administered intravenously for relaxation. Tidal volume was adjusted so that there was good chest expansion using inspiratory pressures between 15 and 20 cm H_2O. Positive end-expiratory pressure was not used.

Arterial P_{CO_2} was maintained between 25 and 30 torr, and intermittent intravenous injections of furosemide, 0.75 mg/kg, were administered throughout the surgery to maintain low intracranial pressure and provide optimal surgical access to the retro-orbital area. The operative position was supine with a slight head-up tilt.

Inspired anesthetic gases were warmed to 37 C and humidified throughout the procedure. The tracheal tube was suctioned hourly to detect and prevent accumulation of secretions, which were watery but not excessive. Intraoperative monitoring included an electrocardiogram, auscultation of breath sounds and heart tones by a precordial stethoscope, manometric central venous pressure measurement, intra-arterial blood pressure monitoring by a radial arterial catheter, and measurement of urine output.

Except for loss of blood, which was replaced using warmed whole blood, fresh frozen plasma, and platelets as necessary, the operation proceeded uneventfully for 12 hours. At this time higher inspiratory pressures were required to deliver acceptable tidal volumes, and the central venous pressure had increased from a base line of 10 cm H_2O to 17 cm H_2O. Breath sounds, although present and equal bilaterally, were diminished and accompanied by mild wheezing. The patient was then ventilated manually to confirm reduced lung compliance, reassess breath sounds, and rule out any mechanical ventilator malfunction. Sterile tracheal tube suctioning yielded minimal secretions; the suction catheter could be passed readily to the carina without obstruction. Furosemide, 10 mg, was administered intravenously and the tracheal tube was changed. This resulted in diminished wheezing but pulmonary compliance showed little improvement. Arterial blood gas tensions at this time showed a pH of 7.24, P_{CO_2} 66 torr, P_{O_2} 67 torr, and base deficit of −1.0 meq/L with 40% oxygen in the inspired air. Small bilateral pneumothoraces were suspected, N_2O was discontinued, and ventilation with 100% oxygen was started. No subcutaneous emphysema was observed, but progressive abdominal distention with tympany suggested that pneumoperitoneum had developed. Intra-operative chest and abdominal x-rays taken at this time demonstrated subcutaneous, mediastinal, retroperitoneal, and peritoneal air. Before controlled abdominal decompression by needle or trocar could be undertaken the patient's condition deteriorated and electromechanical dissociation developed. Rapid subxiphoid laparotomy with immediate decompression of pneumoperitoneum and insertion of a Jackson-Pratt drain restored normal chest wall and pulmonary compliance. Cardiac output and normal sinus rhythm were then rapidly restored by closed cardiac compression plus intravenous calcium chloride, 100 mg, sodium bicarbonate, 40 meq, atropine. 0.3 mg, and ephedrine, 2.5 mg. A temporary feeding gastrostomy tube was also inserted for postoperative nutritional support. The patient's condition stabilized quickly. Arterial blood gas tensions while breathing 100% O_2 were pH 7.40, P_{CO_2} 32 torr, P_{O_2} 240 torr, and base excess +1.0 meq/L. The remaining 3 hours of the operation proceeded uneventfully, and, following pancuronium reversal with atropine and neostigmine, the patient was transferred to the pediatric intensive care unit breathing spontaneously and neurologically responsive. Immediate postoperative chest x-ray demonstrated resolving subcutaneous emphysema, pneumomediastinum without pneumothorax, and pneumoperitoneum (Figure). Over the next several days, subcutaneous, mediastinal, retroperitoneal, and peritoneal emphysema resolved, and the peritoneal drain was removed. The trachea was decannulated on the 7th postoperative day.

Discussion

Prolonged mechanical ventilation through a tracheostomy during lengthy craniofacial reconstruction may result in significant extrapleural air leaks. Pneumomediastinum is common following tracheostomy and may occur alone or be accompanied by subcutaneous emphysema, pneumothorax, or pneumoperitoneum (3, 4).

There are two routes by which air may enter the mediastinum during positive-pressure ventilation following tracheostomy (8, 9). Air escaping from ruptured peripheral alveoli may dissect medially alongside pulmonary vessels to the hilar areas and mediastinum. Typically, alveolar rupture with perivascular air dissection is the result of high airway pressures during mechanical ventilation. Second, and more commonly, air may leak around the tracheostomy site and dissect paratracheally along loose cervical fascial planes to the mediastinum. Positive-pressure ventilation and continuing airway obstruction in the spontaneously breathing patient will each contribute to paratracheal air dissection by generation of high transpleural pressures (8). Development of pneumomediastinum by paratracheal air dissection is more likely in the presence of a new tracheostomy in which cervical fascial planes have been recently disrupted (8).

Pneumomediastinum is, in itself, usually benign as mediastinal pressures seldom become elevated to levels sufficient to produce cardiac tamponade with hemodynamic compromise (9). This is because mediastinal air can easily escape along one of several soft tissue planes producing subcutaneous emphysema, varying degrees of pneumothorax, or, more rapidly, pneumoperitoneum and pneumopericardium (1, 9).

In the present case the prolonged use of positive-pressure ventilation together with a recent tracheostomy is thought to have resulted in cervical air dissection and pneumomediastinum in spite of low mean airway pressures. Once pneumomediastinum had developed, anesthetic gases continued to be forced inward along opened tissue planes by mechanical ven-

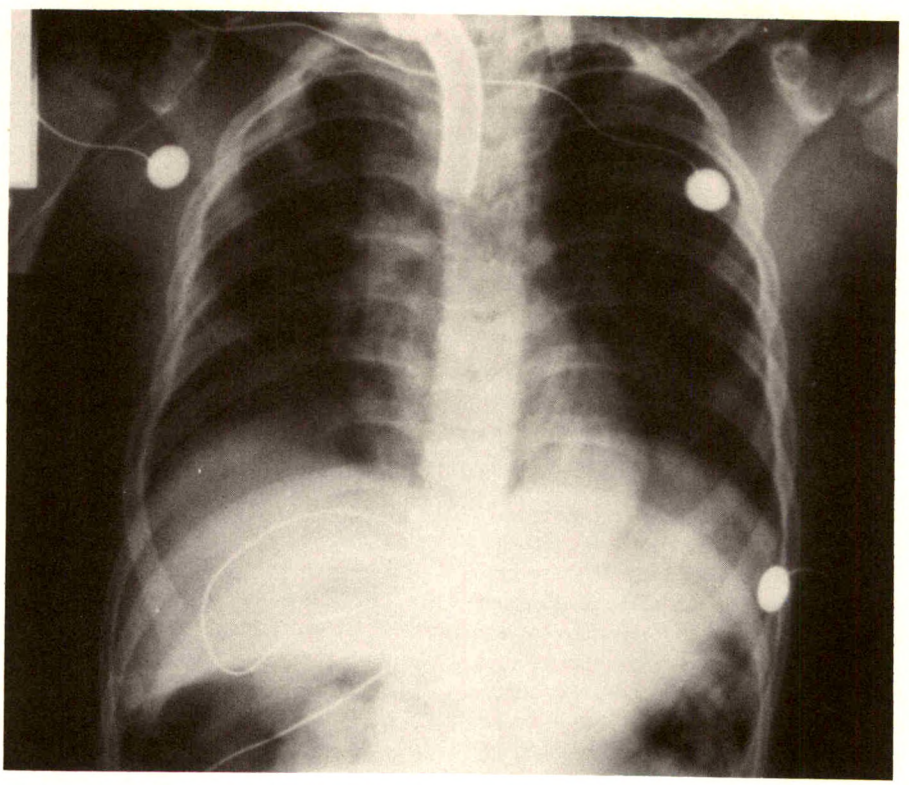


FIGURE. Immediate postoperative chest x-ray demonstrated no pneumothorax, resolving subcutaneous emphysema, pneumomediastinum, and pneumoperitoneum. A Shiley cuffed tracheostomy cannula is in good position above carina.

tilation. These gases then escaped from the mediastinum by dissecting cranially along cervical fascial planes to produce subcutaneous emphysema and also by dissecting caudally along retroperitoneal planes to produce pneumoperitoneum. Pneumothorax did not develop in this patient. However, the buildup of intra-abdominal air, aggravated by the use of N_2O, may have resulted in extreme elevation of the hemidiaphragms which significantly impeded ventilation, decreased thoracic venous return, and reduced cardiac output. Hypercapnia, cardiac dysrhythmia, and hypotension then ensued.

The possibility of pneumomediastinum should be considered in any patient with recent tracheostomy, particularly in children who characteristically have loose cervical areolar tissues that predispose to easy air dissection (10). Pneumomediastinum, although common and usually innocuous, may be a forewarning of more serious sequelae such as pneumothorax or pneumoperitoneum, which would necessitate immediate decompression and continued drainage during and after mechanical ventilation until the air leaks seal (5, 11).

During lengthy surgical procedures in patients with tracheostomies, attention should be directed toward ensuring the continued presence of clear bilateral breath sounds, the absence of subcutaneous emphysema or abdominal distention, and the maintenance of low mean airway pressures. Elective tracheostomies in children undergoing craniofacial reconstruction should be performed primarily for maintenance of the airway rather than for ventilation and, if necessary, should be performed as close to the end of the surgical procedure as possible to avoid barotrauma from prolonged mechanical ventilation. Postoperative radiographic evidence of significant subcutaneous or mediastinal emphysema following tracheostomy should prompt immediate patient evaluation, including an attempt to reduce mean airway pressures and wean the patient from ventilatory support before pneumothorax or pneumoperitoneum can develop (5, 11).

REFERENCES

1. Davies DW, Munro IR. The anesthetic management and intraoperative care of patients undergoing major facial osteotomies. Plast Reconstr Surg 1975;55:50–5.
2. Finucane BT, Brown RG, O'Brien MS. Anesthesia for craniofacial reconstructive surgery. Anesth Rev 1980;7:39–43.

3. Oliver P, Richardson JR, Clubb RW, Flake CG. Tracheotomy in children. N Engl J Med 1962;267:631–7.
4. Gaudet PT, Peerless A, Saski CT, Kirchner JA. Pediatric tracheostomy and associated complications. Laryngoscope 1978;88:1633–41.
5. Zimmerman JE, Dunbar BS, Klingenmaier CH. Management of subcutaneous emphysema, pneumomediastinum, and pneumothorax during respirator therapy. Crit Care Med 1975;3:69–73.
6. Pollack MM, Fields AI, Holbrook PR. Pneumothorax and pneumomediastinum during pediatric mechanical ventilation. Crit Care Med 1979;7:536–9.
7. Posthumus DL, Pierce TH. Fatal tension pneumopericardium complicating tracheostomy. Chest 1978;73:107–9.
8. Padovan IF, Dawson CA, Henschel EO, Lehman RH. Pathogenesis of mediastinal emphysema and pneumothorax following tracheotomy. Chest 1974;66:553–6.
9. Webb WR, Johnston JH, Geisler JW. Pneumomediastinum: physiologic observations. J Thorac Cardiovasc Surg 1958;35:309–15.
10. Bergstrom O, Diamalt H. Mediastinal emphysema complicating tracheostomy. Arch Otolaryngol 1960;71:628–34.
11. Goodman LR, Putman CE. Radiologic evaluation of patients receiving assisted ventilation. JAMA 1981;245:858–60.

Diazepam Premedication Depresses Respiratory Drive

The respiratory effects of premedication with intravenous diazepam were assessed in 10 healthy patients awaiting minor operative procedures. All patients were A.S.A. physical status class I. Mean age (± SD) was 33.5 ± 14.1 years). Measurements were recorded before and 60 minutes after administration of diazepam, 0.14 mg/kg. Mouth occlusion pressure ($P_{0.1}$) was used as an index of neuromuscular inspiratory drive. Minute-ventilation ($\dot{V}_E$), respiratory frequency (f) and mean inspiratory flow rate (V_T/T_I) were significantly reduced after diazepam. During carbon dioxide rebreathing the slopes of $\dot{V}_E$, f, $\dot{V}_T/T_I$ and $P_{0.1}$ with $P_{A_{CO_2}}$ were significantly reduced. These results confirm that diazepam produces significant respiratory depression in healthy subjects. The authors conclude that diazepam used under clinical conditions depresses the respiratory center. (*Clergue F, Desmonts JM, Duvaldestin P, Delavault E, Saumon G: Depression of respiratory drive by diazepam as premedication. Br J Anaesth 1981;53:1059–63*)

ANESTH ANALG
1982;61:150-2

Inadvertent Prolonged Cannulation of the Carotid Artery

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Percutaneous cannulation of the internal jugular vein for placement of central venous catheters is commonplace in the operating room and in critical care areas. This technique is not without complications, and excellent reviews of these mishaps have been compiled by Defalque (1) and Majek et al (2). Carotid artery puncture has been the most frequently reported complication of this procedure (3–5), usually being managed without sequelae. The case reported here describes a cerebral embolism subsequent to prolonged cannulation of the right common artery with a #8 French Cordis introducer.

Case Report

A 46-year-old male patient was transferred to our hospital for treatment of inadvertent carotid artery cannulation. Eight days previously he had suffered an anterior subendocardial myocardial infarction. Due to dysrhythmias and hemodynamic instability, an attempt was made to introduce a pulmonary arterial catheter via the right internal jugular vein, using the anterior approach. The right carotid artery was cannulated with a #8 French Cordis introducer. Pulsatile blood from the introducer led to initial recognition of intra-arterial placement, and the catheter was left in place and capped. Heparinization was commenced, and the patient was transferred to our facility for further evaluation. Seventy-two hours after cannulation, angiography demonstrated that the catheter was lying in the right common artery, projecting to the level of the innominate artery (Figure). An area of decreased dye filling surrounded the catheter, suggesting a thrombus enveloping the 4 cm of catheter within the vessel. Ocular plethysmography showed ophthalmic artery pressures to be 60 mm Hg on the right and 90 mm Hg on the left, consistent with nearly complete right carotid occlusion.

The patient was scheduled for surgical removal of the catheter with distal control of the vessel to prevent thromboembolization into the cerebral circulation. In the operating room, the patient was anesthetized with a nitrous oxide, narcotic, relaxant technique. Monitoring devices included left radial arterial, pulmonary arterial, and Foley catheters, and electrocardiogram (ECG) with V_5 lead. The pulmonary arterial catheter was placed via the left external jugular vein. His intraoperative anesthetic course was unremarkable. The surgical team removed approximately 10 g of thrombus from a visibly inflamed right common carotid artery and extracted the Cordis introducer through an entry site 4 cm superior to the innominate bifurcation. No residual thrombus was noted. After surgery the patient's neurologic examination was normal and his vital signs were stable. He continued to do well until 18 hours after surgery when he had the acute onset of left hemiparesis. A computed tomography (CT) scan showed a pale infarct in the distribution of the middle cerebral artery; ocular plethysmographic pressures were normal, consistent with an embolism rather than proximal arterial occlusion. The patient's course was further complicated by a myocardial infarction 6 days after surgery. The patient was discharged 16 days after surgery to return for physical therapy rehabilitation for his residual hemiparesis.

Discussion

In the 15 years since Hermosura et al (6) initially described internal jugular catheterization for hemodynamic monitoring, numerous complications have been reported. The most common of these is carotid artery puncture, varying in incidence between 0% and 13% in several series (5, 7–9). Although arterial puncture can usually be managed without sequelae, acute (8) and chronic (10) hematomas, neurologic damage (11), cardiac arrest (12), hemothorax (9, 13), and fatalities (9, 13) have been reported. Cerebral embolization after carotid artery puncture has not been previously reported.

In the case described here, arterial puncture, per se, was not responsible for the neurologic catastrophe. Rather, prolonged cannulation of the carotid artery led to thrombus formation and arteritis, with resulting cerebral embolization. Removal of the introducer was delayed in anticipation that coronary artery bypass surgery might be performed concurrently with closure of the carotid arteriotomy. Evaluation of the patient's cardiac disease and other medical problems required 72 hours; surgical removal of the catheter thus did not occur until 96 hours after initial cannulation. Even with systemic heparinization (partial thromboplastin time [PTT] greater than twice base line), thrombus formation was evident at surgery. It is apparent that

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Received from the Department of Anesthesiology, National Naval Medical Center, Bethesda, Maryland 20814. Accepted for publication September 28, 1981.

The views contained herein are those of the author and are not to be construed as those of the Department of the Navy, or as policy of the Department of the Navy.

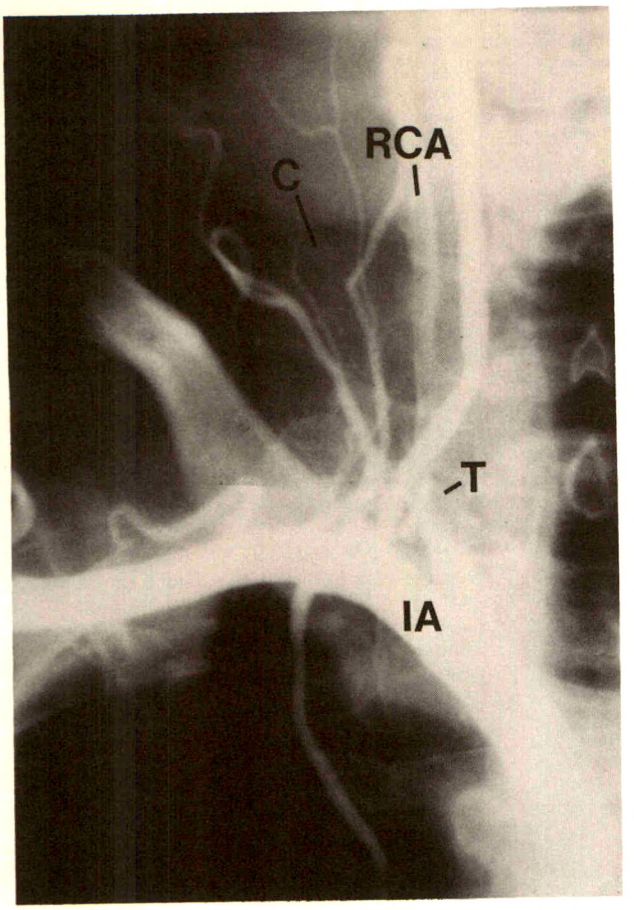


FIGURE. Preoperative angiographic roentgenogram. Note large thrombus in right common carotid artery. C, catheter (#8 French Cordis); RCA, right common carotid artery; IA, innominate artery; T, thrombus.

prolonged carotid arterial cannulation is not desirable even with heparinization. Early intervention is necessary if inadvertent arterial cannulation occurs.

Immediate removal of intra-arterial large-caliber catheters and pressure at the entry site is often adequate to control hemorrhage, but may not always prevent serious complications. Schwartz et al (9) reported five cases in which large-caliber catheters were placed into carotid arteries, four of which had no complications when the catheters were immediately removed and local pressure applied. The fifth patient, however, succumbed to intrathoracic hemorrhage from the arteriotomy. McEnany and Austen (8) found pressure usually effective in preventing hemorrhage after arteriotomy, but reported two cases of hematoma formation in patients who were heparinized during surgery after arteriotomy with 16-gauge catheters. Such nonoperative therapy after removal of large-caliber arterial catheters, although frequently effective, does not reliably prevent untoward consequences from arteriotomy.

If nonoperative therapy is not reliable, are surgical exploration and primary closure of the arteriotomy justified? Schwartz et al (9) recommend that large-caliber catheters be removed with immediate primary closure of the arteriotomy under general anesthesia concurrent with elective surgical procedures. This seems justifiable in patients who sustain arterial cannulation during placement of preoperative monitoring cannulae, as these patients are presumably optimally prepared for surgery and would otherwise be subjected to an anesthetic for their scheduled surgical procedure. However, complications of attempted internal jugular venous catheter placement may occur in critical care settings and situations in which patients are not scheduled for surgery, as in the case reported here. In these patients, who are not prepared for a general anesthetic and who often are at high risk for perioperative complications because of their underlying medical conditions, it is less clear that general anesthesia with immediate surgical closure of an arteriotomy is desirable. It may be possible to perform closure of the carotid arteriotomy under deep or superficial cervical plexus blocks, although the relative risk of such regional techniques compared with general anesthesia has not been critically evaluated. Additionally, alterations of cervical anatomy by hematoma, if present, may make regional landmarks less visible and anesthetic distribution less reliable. It is ironic that critically ill patients, least able to tolerate any complications from inadvertent carotid arteriotomy, are less likely to have surgical closure because of their elevated surgical and anesthetic risks.

The potential severity of complications from large-caliber arterial cannulation argues strongly for the prevention of such mishaps. If the carotid artery must be entered during internal jugular vein location, it should be with the smallest needle possible. We use a 22-gauge "seeker needle" modified from Petty (14) with the approach of Daily et al. (15) and have not had any hematoma formation after arterial puncture with the small needle while locating the internal jugular vein. To establish venous placement, a radial arterial blood sample is compared with the blood aspirated through the seeker needle. Visual comparison is usually adequate, but oximetric measurements may be used in hypoxemic patients to compare the oxygen contents of the samples. Patients breathe 100% oxygen by face mask during this procedure to maximize the arteriovenous oxygen saturation differences. Once venous positioning has been established, larger

catheters are placed, again with comparison with arterial samples to ensure continued venous placement. This procedure minimizes the risk of large-caliber arteriotomy.

If large-caliber catheterization of the carotid artery occurs in spite of the technique described, the risks and benefits of immediate surgical exploration vs nonsurgical therapy should be considered. Delayed removal of the catheter clearly has no place in the management of inadvertent arterial cannulation.

REFERENCES

1. Defalque RJ. Percutaneous catheterization of the internal jugular vein. Anesth Analg 1974;53:116–21.
2. Majek M, Malatinsky J, Kadlik T. Inadverent thoracic duct catheterization during transjugular central venous cannulation: a case report. Acta Anesthesiol Scand 1977;21:320–3.
3. Mostert JW, Hassan MA, Jackson JW. A complication of percutaneous cannulation of the internal jugular vein. Thorax 1972;27:496–9.
4. Brinkman AJ, Costley DO. Internal jugular venipuncture. JAMA 1973;223:182–3.
5. Belani KG, Buckley JJ, Gordon JR, Castaneda W. Percutaneous cervical central venous line placement: a comparison of the internal and external jugular routes. Anesth Analg 1980;59:40–4.
6. Hermosura B, Vanags L, Dickey N. Measurement of pressure during IV therapy. JAMA 1966;195:321–4.
7. Jernigan WR, Gardner WC, Mahr MM, Milburn JL. Use of the internal jugular vein for placement of central venous catheters. Surg Gynecol Obstet 1970;130:520–4.
8. McEnany MT, Austen WG. Life-threatening hemorrhage from inadvertent cervical arteriotomy. Ann Thorac Surg 1977;24:233–6.
9. Schwartz AJ, Jobes DR, Greenhow DE, Stephenson LW, Ellison N. Carotid artery puncture with internal jugular cannulation. Anesthesiology 1979;51:S160.
10. Brown CS, Wallace CT. Chronic hematoma—a complication of percutaneous catheterization of the internal jugular vein. Anesthesiology 1976;45:368–9.
11. Butsch JJ, Butsch WL, DaRosa JTF. Bilateral vocal cord paralysis: a complication of percutaneous cannulation of the internal jugular vein. Arch Surg 1976;111:828–9.
12. Ohligisser M, Kaufman T, Taitelman U. Cardiac arrest following a complication of internal jugular cannulation. Anaesthesia 1979;34:1035–7.
13. Wisehart JD, Hassan MA, Jackson JW. A complication of percutaneous cannulation of the internal jugular vein. Thorax 1972;27:496–9.
14. Petty C. An alternative method for internal jugular venipuncture for monitoring CVP. Anesth Analg 1975;54:157.
15. Daily PO, Griepp RB, Shumway NE. Percutaneous internal jugular vein cannulation. Arch Surg 1970;101:534–6.

ANESTH ANALG
1982;61:153–4

Administration of Anticholinesterase Drugs in the Presence of Beta-Adrenergic Blockade

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The safety of administering an anticholinesterase drug for reversal of non-depolarizing neuromuscular blockade in a patient being treated with a beta-adrenergic antagonist drug such as propranolol is unsettled. Theoretically, beta-adrenergic blockade would result in a predominance of parasympathetic activity at the heart which might be exaggerated by the subsequent administration of an anticholinesterase drug. Indeed, Sprague (1) reported a decrease in the heart rate from 60 to 30 beats per minute following the intravenous administration of neostigmine (2.5 mg) and atropine (1.25 mg) to a patient receiving propranolol (40 mg) every 12 hours for control of supraventricular tachycardia. Prys-Roberts (2) reported that heart rate always decreased to less than 45 beats per minute following administration of neostigmine to patients with renovascular hypertension who were being treated with large doses (10 to 36 mg/kg) of propranolol. On the other hand, we found that bradycardia did not occur following administration of neostigmine to a 55-kg patient with renovascular hypertension who was being treated with 960 mg of propranolol daily (3). Therefore, we designed an animal study to determine whether a reduction in heart rate, premature cardiac beats, or slowing of conduction of the cardiac impulse through the atrioventricular node predictably followed the administration of an anticholinesterase drug plus atropine in the presence of beta-adrenergic blockade.

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Methods

Fifteen mongrel dogs were anesthetized with intravenous thiopental (10 mg/kg) followed by intubation of the trachea and controlled ventilation with 1.0% inspired halothane in oxygen. Intravenous pancuronium (0.15 mg/kg) was also administered at this time. The electrocardiogram was continuously recorded. A femoral arterial catheter was placed to facilitate sampling of arterial blood for measurement of the arterial carbon dioxide partial pressure. The ventilator was adjusted to maintain the partial pressure of carbon dioxide between 35 and 45 torr. Body temperature, as measured with an esophageal temperature probe, was maintained above 36 C by the use of a heating pad. Intravenous fluid replacement was with lactated Ringer's solution administered at a rate of 5 ml/kg/hr.

The heart rate before and after the rapid intravenous administration of isoproterenol (100 μg/kg) was measured 30 minutes after the induction of anesthesia. Heart rate after isoproterenol was calculated from a 15-second portion of the electrocardiogram that was recorded between 60 and 75 seconds after administration of the drug. Propranolol (0.25 mg/kg) was then injected intravenously and the isoproterenol challenge was repeated 10 minutes later. This dose of propranolol is similar to the dose used by other investigators to produce beta-adrenergic blockade in dogs (4). The absence of an increase in heart rate following the injection of isoproterenol confirms the presence of beta-adrenergic blockade (5).

Atropine (30 μg/kg) plus neostigmine (70 μg/kg) (group I, eight dogs) or pyridostigmine (350 μg/kg) (group II, seven dogs) were administered as a rapid intravenous injection 10 minutes after production of the beta-adrenergic blockade. The electrocardiogram was recorded for 60 minutes following administration of the atropine-anticholinesterase mixture. An isoproterenol challenge was administered to group II dogs at the conclusion of this 60-minute observation period.

Analysis of heart rate changes after the isoproterenol challenges was performed using Student's *t*-test. A p value less than 0.05 was considered statistically significant. In addition, the electrocardiogram was examined for the presence of premature atrial or ventricular beats or for an increase in the P-R interval beyond 0.2 seconds that persisted for more than 15 seconds.

TABLE

Heart Rate before and after Administration of Isoproterenol (ISO), Propranolol, and Atropine-Anticholinesterase*

Group	After induction of anesthesia		After propranolol		Minutes after atropine-anticholinesterase					ISO only
	Control	ISO	Control	ISO	1	3	5	30	60	
	beats/min									
I (neostigmine)	129 ± 7	173 ± 10†	109 ± 8	111 ± 7	106 ± 9	106 ± 9	105 ± 6	104 ± 7	106 ± 7	—
II (pyridostigmine)	144 ± 14	179 ± 15†	129 ± 7	129 ± 7	127 ± 6	129 ± 7	127 ± 5	126 ± 8	124 ± 8	126 ± 9

* Values are means ± SE.

† $p < 0.05$ vs corresponding control measurement.

Results

The administration of intravenous propranolol (0.25 mg/kg) during halothane-oxygen anesthesia and pancuronium-induced neuromuscular blockade prevented the increase in heart rate produced by an isoproterenol challenge (100 μg/kg) (Table). This inhibition of the chronotropic effect of isoproterenol by propranolol lasted for at least 60 minutes following the injection of the beta-adrenergic antagonist drug (Table). The administration of neostigmine (group I) or pyridostigmine (group II) plus atropine during persistence of beta-adrenergic blockade did not result in significant slowing of the heart rate (Table). Indeed, bradycardia (arbitrarily defined as a 30% reduction from the heart rate present immediately before administration of the anticholinesterase drug), premature atrial or ventricular beats, or prolongation of the P-R interval beyond 0.2 seconds did not occur in any animal.

Discussion

Beta-adrenergic blockade, as produced by propranolol, results in unopposed parasympathetic activity at the heart. It has been suggested that exaggerated vagotonic responses can occur when an anticholinesterase drug is administered for reversal of neuromuscular blockade in patients being treated with propranolol (1, 2). Indeed, it has been recommended that persistent neuromuscular blockade in a patient being treated with a beta-adrenergic antagonist drug should be managed with continuation of mechanical ventilation (6). Our data do not support this recommendation. Specifically, the present data do not demonstrate the occurrence of an exaggerated parasympathetic response when neostigmine or pyridostigmine is administered in the presence of beta-adrenergic blockade. In fact, heart rate slowing or prolongation of the P-R interval on the electrocardiogram did not occur in the presence of beta-adrenergic blockade in any dog receiving an anticholinesterase drug. Persistence of beta-adrenergic blockade following administration of the anticholinesterase drug was confirmed by the absence of a chronotropic effect of isoproterenol at the conclusion of the study period.

Differences in the muscarinic effects of anticholinesterase drugs might influence the responses observed when these drugs are administered in the presence of beta-adrenergic blockade. For example, pyridostigmine is alleged to have less muscarinic effect on the heart than neostigmine (7). Conceivably, this could protect against exaggerated heart rate slowing when this anticholinesterase drug is administered in the presence of beta-adrenergic blockade. Indeed, reports of severe bradycardia in patients receiving propranolol (1, 2) followed administration of neostigmine rather than pyridostigmine. Nevertheless, the present data do not demonstrate any difference between the heart rate responses observed following the administration of neostigmine or pyridostigmine in the presence of beta-adrenergic blockade.

Based on these data, we conclude that exaggerated heart rate slowing or other adverse cardiac effects do not follow the administration of anticholinesterase drugs in the presence of beta-adrenergic blockade. Therefore, reversal of non-depolarizing neuromuscular blockade with neostigmine or pyridostigmine combined with atropine seems acceptable in patients being treated with propranolol.

REFERENCES

1. Sprague DH. Severe bradycardia after neostigmine in a patient taking propranolol to control paroxysmal atrial tachycardia. Anesthesiology 1975;42:208–10.
2. Prys-Roberts C. Hemodynamic effects of anesthesia and surgery in renal hypertensive patients receiving large doses of β-receptor antagonists. Anesthesiology 1979;51:S122.
3. Stoelting RK. Halothane-nitrous oxide anesthesia in a patient receiving high dose propranolol. Anesthesiology 1979;50:546–7.
4. Horan BF, Prys-Roberts C, Hamilton WK, Roberts JG. Haemodynamic responses to enflurane anaesthesia and hypovolaemia in the dog and their modification by propranolol. Br J Anaesth 1977;49:1189–97.
5. Mèrin RG, Tonnesen OS. The effect of beta-adrenergic blockade on myocardial haemodynamics and metabolism during light halothane anaesthesia. Can Anaesth Soc J 1969;16:336–44.
6. Warner WA. Beta adrenergic blocking agents and anaesthesia: a review. Can Anaesth Soc J 1968;15:42–5.
7. Randall LO. Pharmacology of the anticholinesterase drugs Mestinon, Prostigmine, Tensilon and TEPP. Am J Med 1955;19:673–8.

ANESTH ANALG
1982;61:155–9

Chloroprocaine Neurotoxicity: Four Additional Cases

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Four cases of prolonged neural blockade following epidural block or unintentional subarachnoid injection of the local anesthetic drug(s) while attempting this block have been reported (1, 2). In three of the patients chloroprocaine alone was injected; in the fourth patient bupivacaine was administered for the test dose and the initial dose, chloroprocaine being used as a reinforcing (refill, top-up) dose. Speculation as to the etiology and the role of chloroprocaine has ensued (1–9).

This article reports four additional similar cases, discusses other possibilities for the neuropathies, and cites documented formulation changes of chloroprocaine from the first clinical investigation published in 1952 (10).

Case Reports

Case 1

In 1977, a white woman, age 40, weight 55 kg, height 165 cm, with an A.S.A. physical status of I, was to have surgery for a knee injury. Before anesthesia her blood pressure was 110/72 torr, heart rate was 68 beats per minute, and respirations were 12 breaths per minute. Intravenous fluids were started. Because the extent of surgery was questionable, the anesthesiologist placed plastic tubing in the caudal canal using an aseptic technique and a single-use (disposable) tray. No trauma (paresthesias, etc.) occurred during performance of the block. Aspiration for blood and cerebrospinal fluid (CSF) was negative. A 3-ml test dose of 3% chloroprocaine (90 mg) with epinephrine 1:200,000 (0.015 mg) showed no evidence of an intravascular or a subarachnoid injection after a time lapse of 3 minutes. Therefore, 24 ml of the solution (720 mg of chloroprocaine and 0.12 mg of epinephrine) was injected. Analgesia to the fourth thoracic dermatome resulted, with a blood pressure of 80/40 torr, a heart rate of 60 beats per minute, and respirations present but not recorded. No treatment was judged necessary for the decrease in blood pressure.

Forty-five minutes later analgesia was still present, but it had become apparent that the duration of the surgery would exceed the duration of the anesthesia from chloroprocaine. After aspiration for blood and CSF and a test dose of 2 ml of 0.75% bupivacaine (15 mg) without epinephrine were negative, the analgesia was reinforced with 12 ml of bupivacaine 0.75% (150 mg) without epinephrine. Fifteen minutes later, analgesia to the third thoracic dermatome, with a blood pressure of 80/40 torr and heart rate of 60 beats per minute, were recorded. Immediately after surgery (the procedure lasted 2 hours and 15 minutes), the blood pressure was 100/60 torr, heart rate was 78 beats per minute, and respirations were 14 breaths per minute. One and a half hours later, the level of analgesia had receded to the tenth thoracic dermatome, and it continued to recede during the night. The next day the patient could move her legs but had numbness of the perineum, which persisted. Thirty days later, myelography was negative, as was a sample of CSF, except that the protein was "slightly elevated," that is 67 mg/100 ml (normal 20 to 60 mg/100 ml). Four years following the procedure, the patient still complains of pain in the coccygeal area, difficulty in controlling urine and feces (principally urine), and no sensation during sexual intercourse. These complaints have been confirmed by urologic and neurologic examinations.

Case 2

In 1976, a white woman, age 30, weight 122 kg, height 165 cm, with an A.S.A. physical status of I, was admitted for vaginal delivery. The delivery was to be followed by tubal ligation. Before anesthesia, intravenous fluids were started. The patient's blood pressure was 140/90 torr, heart rate was 100 beats per minute, and respirations were 16 breaths per minute. Using an aseptic technique and a single-use tray, the anesthesiologist placed plastic tubing in the caudal canal. No trauma (paresthesia, etc.) occurred during insertion of the catheter. Aspiration for blood and CSF was negative. A 4-ml test dose of 0.25% bupivacaine (10 mg) without epinephrine showed, after 2 minutes, no evidence of an intravascular or a subarachnoid injection. Therefore, 22 ml of the same solution (55 mg of bupivacaine) was injected. No evidence of a subarachnoid block ensued, and anesthesia was satisfactory for the vaginal delivery (the dermatome level was not recorded). Blood pressure, heart rate, and respirations were 130/90 torr, 80 beats per minute, and 16 breaths per minute, respectively, before and during delivery. Following delivery, approximately 1 hour and 15

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minutes after the initial injection, analgesia was inadequate for the tubal ligation. Aspiration for blood and CSF was negative, and 22 ml of 2.0% chloroprocaine (440 mg) without epinephrine was injected. Within 10 minutes, the patient was dyspneic and then apneic, and respirations were controlled for 1½ hours using an anesthesia machine and face mask. When apnea occurred, aspiration from the plastic tubing yielded 6 ml of fluid. When respirations returned, another 5 to 6 ml of fluid could be aspirated. Laboratory analysis of these samples confirmed the impression that the aspirated fluid was CSF. The level of analgesia slowly receded during the next 48 hours.

At that time, the neurologic examination revealed "spinal signs and symptoms gradually resolving but [there was] residual paresis of lower extremities and dyasthesia to midthigh and to midabdomen level." Four years later the patient is ambulatory, but with bladder dysfunction (urgency and frequency), difficulty with control of bowels, no sensation during sexual intercourse, and loss of sensation in the buttocks, thighs, and back of legs.

Case 3

In 1980, a white woman, age 31, weight 66 kg, height 168 cm, with an A.S.A. physical status of I, had had an uneventful, spontaneous delivery the previous day. An episiotomy and repair were performed with local infiltration of 1.0% lidocaine. She elected to have a tubal ligation the following day under lumbar epidural block. Intravenous fluids were started. Her blood pressure was 120/70 torr, heart rate was 82 beats per minute, and respirations were 17 breaths per minute. No premedication was administered. Using an aseptic technique and a single-use regional block tray, the anesthesiologist placed a 19-gauge needle in what was thought to be the epidural space. No trauma (paresthesias, etc.) occurred during placement of the needle. Aspiration tests for blood and CSF were negative. A test dose of 3 ml of 3.0% chloroprocaine (90 mg) with 1:200,000 epinephrine (0.015 mg) showed, after 3 minutes, no evidence of an intravascular or a subarachnoid injection. Therefore, 20 ml of the same solution (600 mg of chloroprocaine with 0.1 mg of epinephrine) was injected. Within 5 minutes the patient complained of difficulty in breathing and therefore respirations were assisted by bag and mask. Eventually the level of analgesia was estimated to be at the third cervical dermatome and a tracheal tube was inserted and respirations were controlled. The lowest blood pressure recorded was 90/62 torr, and heart rate was 80 beats per minute. Following tubal ligation, a ventilator was used in the postanesthetic recovery unit for artificial ventilation. Approximately 2 hours following the apparent almost total spinal anesthesia, she was beginning to respond, and 30 minutes later the tracheal tube was removed. Within 1 hour, the level of analgesia was judged to be at the third thoracic dermatome. Four hours later, the patient could move the lower extremities. The next day she was ambulatory, with tingling of the lower extremities, decreased bladder and rectal sensation, and tingling in the perineum. Approximately 10 months later she is still having difficulty controlling urine and feces and has no sensation during sexual intercourse.

Case 4

In 1980, a white woman, age 34, weight 74 kg, height 159 cm, with an A.S.A. physical status of I, was to have a laparoscopy. Intravenous fluids were started. Her blood pressure was 120/80 torr, heart rate was 70 beats per minute, and respirations were 12 breaths per minute. Using an aseptic technique and a single-use tray, the anesthesiologist placed a 19-gauge needle in what was thought to be the epidural space. No trauma (paresthesias, etc.) occurred during placement of the needle. Aspiration for blood and CSF was negative. A test dose of 3 ml of 3.0% chloroprocaine (90 mg) with 1:200,000 epinephrine (0.015 mg) revealed, after 3 minutes, no evidence of an intravascular or a subarachnoid injection. Therefore, 18 ml of the same solution (540 mg of chloroprocaine with 0.09 mg of epinephrine) was injected. Within 4 minutes total spinal anesthesia resulted. The patient became apneic and so was immediately intubated and ventilated. Blood pressure was 90/80 torr, and heart rate was 76 beats per minute. Approximately 1½ hours later the level of analgesia was at the third thoracic dermatome, and she was extubated. The level of analgesia receded over the next 24 hours, but she had hypalgesia and paresis of the legs and required an indwelling urinary catheter. Four weeks later she was able to walk, but had loss of sensation of the perineum and still required an indwelling urinary catheter. One year later she has loss of perineal sensation, no sensation during sexual intercourse, positive left and right Babiniski reflexes, and clonic left and right Achilles tendon reflexes.

Discussion

The etiology of neuropathies following spinal and epidural block has been extensively reviewed, and has been attributed to many factors (7, 11–16). Articles describing these neuropathies lack, however, documentation of the facts needed to pinpoint the etiology such as: (*a*) a neurologic and other appropriate consultation; (*b*) the pertinent details of the anesthesia (technique, the drug(s) used, type of equipment, and so forth); and (*c*) the patient's physical status before, during, and following anesthesia. Conversely, our cases and the four previously reported ones (1, 2) seem to rule out most, if not all, of the potential causes of neuropathy other than the local anesthetic solution(s). Nonetheless, whether chloroprocaine is the common factor in the four cases previously reported has been questioned (7–9) with emphasis that no formulation changes have occurred since 1964 (9). As yet all the variables of these neuropathies (e.g., epinephrine content of the solutions, total milligram dose of the local anesthetic drug, slowing of detoxi-

fication of chloroprocaine by other local anesthetic drugs, and changes in formulation of chloroprocaine) have not been systematically studied.

Epinephrine alone as a cause of neuropathy is unlikely. From 1947 through 1980 in more than 25,000 patients, one of the authors (D.C.M.) and his associates have added 0.2 mg of epinephrine (0.2 ml of 1:1000) to proper doses of tetracaine, lidocaine, dibucaine, and bupivacaine solutions for spinal anesthesia without encountering any cases of neuropathy. Animal investigation supports that the likelihood of neuropathy resulting from the subarachnoid injection of epinephrine is infinitesimal (17). Also, in 1952, in a study of 84 patients who received subarachnoid injections of 100 mg of chloroprocaine (3.3% solution) containing epinephrine no neuropathies were reported (10).

All local anesthetic drugs in high enough concentrations are neurotoxic. Interestingly, in the four previously reported cases, the total milligram doses of chloroprocaine administered were 360, 480, and 540 mg without epinephrine and 840 mg with 1:200,000 epinephrine (1, 2). The patient who received 360 mg had evidence of neuropathy for 72 hours and none thereafter. The others had prolonged neuropathy, and whether they ever completely resolved could not be ascertained from the reports. One of our patients received a total dose of 440 mg of chloroprocaine without epinephrine, and, the others, doses of 630, 690, and 810 mg with epinephrine 1:200,000. All have residual neuropathy. In the past, up to 200 mg of chloroprocaine subarachnoidally resulted in no neuropathy (10, 18, 19). From 1952 through 1980 at the institution in which one of the authors (D.C.M.) practices, four cases of unintentional subarachnoid injection of chloroprocaine have occurred, one reported (19), and three unreported. The dosages in the unreported cases ranged up to 400 mg of a 2.0% solution. In two of these, no evidence of neuropathy resulted, but one patient, who received 400 mg, had evidence of neuropathy (difficulty in walking) which resolved in 96 hours. Therefore, the milligram dose of chloroprocaine in humans at which no permanent neuropathy occurs appears to be more than 200 mg but less than 400 mg. Using repeated fractional doses in an intermittent-injection technique in order to avoid the unintentional injection of a large dose into the subarachnoid space has been suggested (3). However, this does not solve the problem of a single-injection technique (cases 2 and 3) or the problem that arises in an intermittent-injection technique if a large reinforcing dose is injected to provide immediate pain relief when partial analgesia exists from a previous dose (cases 1 and 2).

In case 1, chloroprocaine was injected before, and in case 2 after, the injection of bupivacaine. As a result, two questions arise. Which drug was responsible? And, could interaction between these drugs be a factor in the neuropathy? The amide local anesthetic derivatives, especially bupivacaine and etidocaine, inhibit the rapid detoxification of chloroprocaine in blood (20). Perhaps in these two cases interaction between the local anesthetic drugs might have been the etiology of the neurotoxicity. Therefore, until this possibility is resolved and in order to minimize confusion when a complication (systemic toxicity, tissue damage, etc.) results, we submit that the common practice of compounding two local anesthetic drugs in a single injection technique or the use of one drug followed by another in an intermittent injection technique be avoided whenever possible.

In cases 2 to 4, unintentional subarachnoid injection of a large dose of chloroprocaine, probably 440 to 600 mg, occurred. But in case 1, as in two of the previously reported cases (1), there was no evidence of such an injection. In these cases, perhaps the effect of chloroprocaine on the spinal cord or the roots of the spinal nerves should be suspected as a possible cause of neuropathy because it, as with all other local anesthetic drugs placed epidurally, can be found in anesthetic concentrations in the CSF (21). Conversely, chloroprocaine, 100 mg, has been administered purposely for spinal anesthesia to 214 patients, and up to 400 mg unintentionally in others, without permanent sequelae (1, 10, 18, 19).

Changes in pH and formulation have occurred since chloroprocaine was introduced in 1952. In 1952, its crystals were dissolved in 0.9% sodium chloride for peripheral nerve blocks (219 patients, 146 with epinephrine) or 10% dextrose for spinal anesthesia (214 patients, 84 with epinephrine) (10). The pH of the 1.0% and 2.0% solutions for peripheral nerve blocks were 4.8 and 4.9, respectively (10). The pH of the spinal solution was not given. Evidently from then through 1956 no pH or formulation changes occurred, because in 1956 chloroprocaine crystals were dissolved in 5.0% dextrose to produce a 2.0% solution, and 18 to 20 ml (360 to 400 mg) of this concentration was used for epidural block in 55 outpatients (18). Interestingly, one of the previously noted unintentional subarachnoid injections occurred in that investigation with no sequelae (18). By 1957, chloroprocaine was included in the *Physicians' Desk Reference*, and a formulation change occurred. The crystals had

apparently been supplanted by 1.0%, 2.0%, and 3.0% solutions without epinephrine (22). From 1959 to 1963, 1.0%, 2.0%, and 3.0% solutions with and without epinephrine were available, and another formulation change had occurred (22). From 1963 through 1970, only 1.0% and 2.0% solutions without epinephrine were marketed, with instructions "not be used for caudal or epidural block" (22). The reasons for such limitations have yet to be revealed. From 1957 through 1970, no information regarding the formulation changes of chloroprocaine (pH and additives) was available, except that in 1967 and 1968 solutions of chloroprocaine contained 2 mg/ml of sodium bisulfite (antioxidant) and 1 mg/ml of methylparaben (preservative) (22). In 1965, the use of chloroprocaine for intravenous regional anesthesia in humans resulted in tissue toxicity, that is, thrombophlebitis in 4% to 8% of cases (23, 24). The etiology of these was never determined. If at that time the solution of chloroprocaine contained the two stated additives, the question arises: was the cause of the thrombophlebitis one or both of these additives, the chloroprocaine, or a combination of all three? In 1971, the presently available formulations of 1.0%, 2.0%, and 3.0% chloroprocaine solutions were introduced (22). Methylparaben was removed from the 2.0% and 3.0% solutions, which were marketed for epidural and caudal anesthesia as Nesacaine-CE. From then until now it has been stated that chloroprocaine does "not injure nervous tissues and is not irritating to other tissues in concentrations employed for infiltration, regional, caudal and epidural anesthesia" (22). The previously reported cases as well as the four cited herein seem to refute this statement (1, 2).

Finally, the neuropathies associated with the use of chloroprocaine in humans surfaced in 1980 and all occurred in a 5-year period (1976 to the present). Furthermore, unlike previously reported cases of neuropathies involving other local anesthetic drugs, neuropathies associated with chloroprocaine are well documented and chloroprocaine seems to be the common constant factor involved. Therefore, until the etiology of neuropathy associated with its use in humans is specifically identified (animal data, because of species differences, can not be extrapolated to humans), and regardless of the statements of other anesthesiologists to the contrary (25, 26), the authors of this article support the decision of those who have suspended its use (27, 28).

ADDENDUM

Case 5 (Seen November 30, 1981). In 1979, a white male, age 53, weight 81 kg, height 175 cm, A.S.A. physical status I, received an epidural block with 20 ml of 3% chloroprocaine (600 mg) without epinephrine for inguinal herniorrhaphy. Within 10 minutes hypoventilation and hypotension occurred, requiring intubation and intravenous ephedrine sulfate. In 1 hour 45 minutes he was extubated. Nine hours later, when the effects of the drug were judged to have dissipated, the patient had: (1) weakness of the legs; (2) perineal pain and numbness; (3) bladder atonicity requiring catheterization; and (4) bowel dysfunction. The leg weakness resolved in 2 weeks. After 2 years, the patient still experiences: (1) pain in the perineum, over the coccyx, and down the legs; (2) tingling of the posterior surface of thighs and calves; (3) bowel dysfunction; (4) no sensation of climax; (5) poor emptying of the bladder, with a residual of 100 to 200 ml; and (6) hypalgesia of the first to the fifth sacral nerves.

REFERENCES

1. Ravindran RS, Bond VK, Tasch MD, Gupta CD, Leurssen TG. Prolonged neural blockade following regional analgesia with 2-chloroprocaine. Anesth Analg 1980;59:447–51.
2. Reisner LS, Hochman BN, Plumer MH. Persistent neurologic deficit and adhesive arachnoiditis following intrathecal 2-chloroprocaine injection. Anesth Analg 1980;59:452–4.
3. Covino BG, Marx GF, Finster M, Zsigmond EK. Prolonged sensory/motor deficits following inadvertent spinal anesthesia. Anesth Analg 1980;59:399–400.
4. Friedman G, DeFazio C. Prolonged neural blockade following regional anesthesia with 2-chloroprocaine. Anesth Analg 1980;59:810.
5. Barsa JE, Batra M, Fink BR. Prolonged neural blockade following regional anesthesia with 2-chloroprocaine. Anesth Analg 1980;59:810–11.
6. McLeskey CH. pH of local anesthetic solutions. Anesth Analg 1980;59:892–3.
7. Kane RE. Neurologic deficits following epidural and spinal anesthesia. Anesth Analg 1981;60:150–61.
8. Govier WM. Cytotoxicity of local anesthetics. Anesth Analg 1981;60:168–9.
9. Gundersen K, Riggi S. Nesacaine® update. Rochester, NY: Pennwalt Corp, Pennwalt publication no. 501 A 301 25M, June 1981.
10. Foldes FF, McNall PG. 2-chloroprocaine: new local anesthetic agent. Anesthesiology 1952;13:287–96.
11. Moore DC. Complications of regional anesthesia. Springfield, IL: Charles C Thomas, 1955:202–25.
12. Lund PC. Peridural analgesia and anesthesia. Springfield, IL: Charles C Thomas, 1966:287–90.
13. Dawkins CJM. An analysis of the complications of extradural and caudal block. Anaesthesia 1969;24:554–63.
14. Moore DC. Complications of regional anesthesia. In: Bonica JJ, ed. Regional anesthesia: recent advances and current status: clinical anesthesia series, Philadelphia: FA Davis Co, vol 2, 1969:228.
15. Usubiaga JE. Neurological complications following epidural anesthesia. Int Anesthesiol Clin 1975;15–31.
16. Bromage PR. Epidural analgesia. Philadelphia: WB Saunders, 1978:666–98.
17. Wu JJ, Harnagel DLA, Brizzee KR, Smith SM. Neurologic effects following intrathecal administration of vasoconstrictior drugs in Rhesus monkeys. Anesthesiology 1954;15:71–88.
18. Colavincenzo JW, Foldes FF, McNall PG, Friday RH. The use of 2-chloroprocaine for epidural block in outpatients. Pa Med 1956;59:338–340.
19. Nellermoe CW, Moore DC, Bridenbaugh LD, Casady GN, Braly B. A clinical appraisal of 2-chloroprocaine in continuous caudal obstetrical anesthesia. Anesthesiology 1960;21:269–72.
20. Lalka D, Vicuna N, Burrow SR, et al. Bupivacaine and other amide local anesthetics inhibit the hydrolysis of chloroprocaine by human serum. Anesth Analg 1978;57:534–9.

21. Krumperman LW, Meschlter SC, Close EL, Wester MR, Erickson KC, Strenge JK. Transdural diffusion of 2-chloroprocaine hydrochloride in man. Anesth Analg 1960;39:55–8.
22. *Physician's Desk Reference.* Oradell, NJ: Medical Economics Company, 1957:494; 1958:702; 1959:713; 1960:722–3; 1961:639; 1962:867–8; 1963:917; 1964:939; 1965:957; 1966:993; 1967:1105; 1968:1132; 1969:1199; 1970:1317–8; 1971:1348–9; 1972:1389–90; 1973:1092–3; 1974:1130–1; 1975:1152–3; 1976: 1191–2; 1977: 1216–7; 1978:1289–90; 1979:1329–30; 1980:1352–3; 1981:1397–8.
23. Harris WH, Slater EM, Bell HM. Regional anesthesia by the intravenous route. JAMA 1965;194:1273–6.
24. Dickler DC, Friedman PL, Susman IC. Intravenous regional anesthesia with chloroprocaine. Anesthesiology 1965;26:244–5.
25. Pue FA, Wahab GM. Fast action vs hasty conclusions. Newsl Soc Obstet Perinatol 1981;12(3):2.
26. Gutsche BB. Hot topic, cooler minds. Newsl Soc Obstet Perinatol 1981;12(4):2.
27. Gibbs CP, Munson ES. Local anesthetic toxicity. Anesth Analg 1980;59:955.
28. Reisner LS. Nesacaine is out. Newsl Soc Obstet Perinatol 1981;12(2):6.

Treating Bupivacaine-Induced Arrhythmias

Nodal and ventricular arrhythmias, along with intraventricular conduction defects, appeared in 34 of 36 cats after approximately 70% of a convulsant dose of bupivacaine was infused at a rate of 1 mg/kg/min. Five minutes after completing double the convulsant dose of bupivacaine (11.8 ± 2.2 mg/kg), a benzodiazepine was given intravenously to arrest convulsions. In 28 cats, the cardiac rhythm converted spontaneously to sinus within the next 20 minutes. In the six cats with persistent arrhythmias, one had ventricular tachycardia following diazepam, 2 mg/kg; the rhythm converted to sinus when lidocaine, 2.5 mg/kg, was given 10 minutes later. The other five cats were given lidocaine, 2.5 mg/kg, 30 minutes after the benzodiazepine. In four of the five, the rhythm converted to sinus after one or two lidocaine boluses. The fifth cat had sinus flurries that reverted to nodal rhythm after each of four lidocaine boluses. Lidocaine did not precipitate hypotension or induce fresh convulsions. (*de Jong RH, Davis NL: Treating bupivacaine induced arrhythmias: preliminary report. Regional Anesth 1981;6:99–103*)

letters TO THE EDITOR

Gas Embolism Associated with Use of Lasers for Urethral Surgery

To the Editor:

The neodymium ytrium aluminum garnet laser (NdYAG) has been used experimentally (1) and clinically (2) for urologic procedures, and it is likely to gain wider acceptance as it provides minimal bleeding and scarring. It involves the injection of carbon dioxide (CO_2) into the urethra under pressure, to provide the surgeon with a clear field of vision. The technique, therefore, involves the risk of gas embolism, a well known complication of urologic procedure (3).

We recently encountered two such complications which occurred in a series of 10 patients.

A healthy male patient was operated on for urethral stricture under light thiopental-nitrous oxide (N_2O)-halothane anesthesia with spontaneous respiration. Following the injection of CO_2 within the urethra, the patient showed the classic signs of gas embolism: deep, gasping respiration, and cyanosis, followed by cardiovascular collapse and cardiac arrest. He was treated by external cardiac massage, vasopressors, and bicarbonate, with cardiovascular recovery. He remained in deep coma but went on to complete recovery.

Another healthy patient was operated on for urethral stricture under thiopental, muscle relaxants, and N_2O anesthesia with controlled ventilation. Following CO_2 injection within the urethra the patient became cyanotic and cardiac arrest occurred. He was immediately treated by external cardiac massage, vasopressors, and bicarbonate with complete recovery within 30 minutes.

These two cases show the potential danger of NdYAG laser surgery in urology, and should warn both surgeons and anesthetists against its complications. Although a suprapubic bladder catheter had been inserted in both cases as a safety device against development of excessive gas pressure that might pour CO_2 into the pelvic veins, gas embolism nevertheless occurred.

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REFERENCES

1. Bullow H, Bullow Y. Preliminary report on endoscopic urethrotomy in a dog using a Nd-YAG laser. Endoscopy 1977;9:44.
2. Bullow H, Bullow Y. Transurethral laser urethotomy in man: Preliminary report. J Urol 1979;121:286–7.
3. Goddard DW, Moffet JD. Fatal air embolism during urologic operation. J Urol 1955;73: 613–8.

Anesthesia Circuit Tube Support Strap

To the Editor:

During maxillofacial surgery, one of the main problems is movement of the head and neck due to manipulations by the surgeons. This requires a good fixation of the circuit tubing on the forehead of the patient to prevent disconnection or too much movement of the nasotracheal tube. The usual method of fixing these tubes is to put folded towels on the forehead and fix the circuit tubing over it with a broad cloth tape circled around the head. This is a cumbersome method and in spite of good fixation, tubes can slip away during the manipulations occurring during surgery.

We modified the arm restraint (manufactured by Boehringer Laboratories) by attaching two 16-cm long and 2.5-cm wide strips of Velcro on one side (for extra grip on the strap)

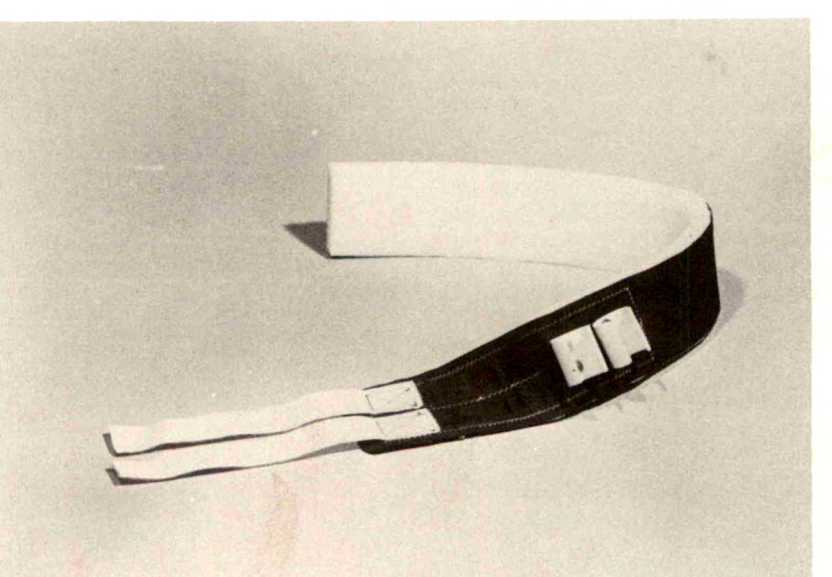


FIG 1. Modified arm restraint used for fixation of circuit tubing.

and attaching two plastic holders which were made of 2.6-cm diameter plastic pipe and slit on one side. Each holder is 2.7-cm long and fixed on the strap side by side as shown in Fig 1. The strap is lined with a disposable piece of foam pad. We developed this strap to improve the fixation of the circuit tubes. The foam lining on the strap, which gives an extra grip on the skin of the forehead without causing undue pressure, can be changed for each patient. We have used this strap on 20 patients and found it to be convenient for the surgeon as well as the anesthesiologist as this strap gives more stability to the circuit tubes as well as to the nasotracheal tube (Figs 2 and 3).

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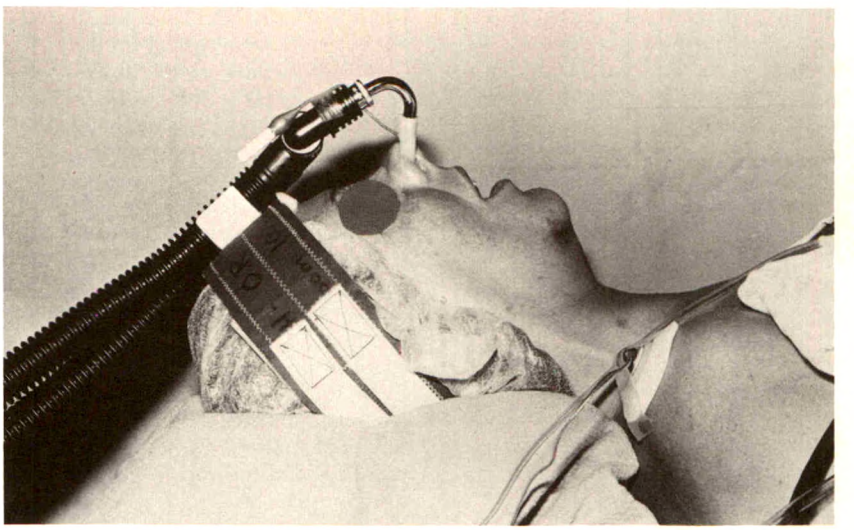


FIG 2. Side view of anesthesia circuit tube support strap.

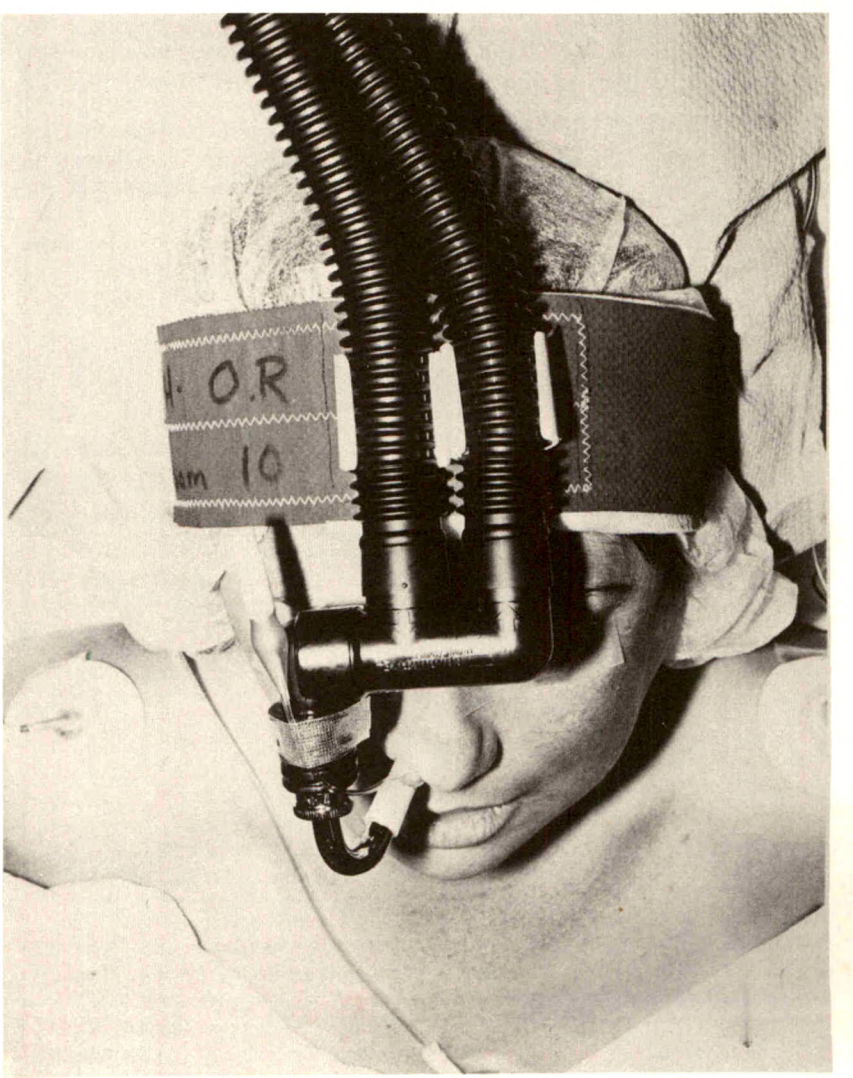


FIG 3. Overhead view of anesthesia circuit tube support strap.

Tracheal or Endotracheal Tubes?

To the Editor:

I have previously expressed my concerns with the terminology being used to describe anesthesia equipment. At the 1968 London Meeting of International Standards Organization Technical Committee 121, Subcommittee on Terminology, Dr. Börje Hallén of Stockholm pointed out the confusion created in the minds of non-English-speaking anesthesiologists by our use of the term endotracheal tube. Dr. Hallén correctly pointed out that we did not have an exotracheal tube so why should we have an endotracheal tube? We also do not use an endogastric tube or an endourethral catheter. It was agreed by the International Committee, after being championed by the British representatives, to use the simple term, tracheal tube.

I am now disturbed to see the abbreviations ET and ETT currently being used in both scientific writings and in the advertising copy appearing in our anesthesia journals. I assume

the abbreviation is being used for endotracheal tube and not exotracheal tube. It seems that chronic abbreviators now have the choice between ETT, ET, and TT. I suggest we stop confusing ourselves and the rest of the world and adopt the use of the standard simple term tracheal tube for this common device.

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(A well taken point, but don't we still administer endotracheal anesthesia? Ed.)

Direct Cardiac Index Determination Using a Thermodilution Computer

To the Editor:

Measurement of cardiac output (CO) has become popular for evaluating the hemodynamic status of patients with cardiac disease. This popularity is in part due to the thermodilution technique which allows easy, rapid determinations of CO. Commercially available computers calculate CO by integrating changes in pulmonary artery blood temperature with time following the rapid intravenous injection of a known volume of cold solution into the right atrium. This measurement is electronically entered into the denominator of the Stewart-Hamilton equation

$$CO = \frac{1.08C_T(60)V_I(T_B - T_I)}{1.22 \int_0^T \Delta T_B(t)dt}$$

Most computers condense the first four constant factors ($1.08 \times C_T \times 60 \times V_I$) of the equation into a computation constant (CC) which is mechanically entered into the computer before determination of CO by thermodilution. As cardiac index (CI) is calculated by dividing CO by body surface area (BSA) (a constant factor) we speculated that the computer would calculate CI directly if the CC that was entered into the computer was the number obtained from dividing the CC by BSA. Although direct CI determination by the computer using this method seems straightforward, the manufacturer does not discuss the validity of this method in the computer product information.

To test our hypothesis we determined CI by two different methods in 10 patients undergoing coronary artery bypass graft surgery. The CI was determined in random sequence by measuring CO using a thermodilution computer (American Edwards Laboratories model 9520) programmed with the CC recommended by the company and then dividing by BSA (method A) or the CC was divided by the BSA and this factor entered into the computer before measurement of cardiac output such that the digital readout reflected cardiac index (method B). All measurements were made following the induction of anesthesia and before the surgical skin incision. Injectate characteristics of 5% dextrose in water (10 ml, 0 to 1 C) and rate of injection (less than 4 seconds) were similar for each method. Cardiac output was measured in triplicate using each method.

Our results are summarized in the Table. The CI determinations were 2.11 ± 0.20 L/min/m^2 (method A) and 2.12 ± 0.22 L/min/m^2 (method B). Using Student's *t*-test for paired data, these results were not statistically different ($p > 0.10$).

TABLE

Individual Cardiac Index (CI) Determinations

Patient no.	Cardiac index*	
	Method A	Method B
	L/min/m²	
1	1.42	1.42
2	3.13	3.36
3	3.05	2.96
4	2.56	2.72
5	1.24	1.28
6	1.87	1.83
7	1.80	1.79
8	2.24	2.24
9	1.70	1.60
10	2.04	2.01
Mean	2.11	2.12
±SEM	±0.20	±0.22

* CI represents mean value obtained from three measurements. Determinations were made by dividing cardiac output by body surface area (BSA) after computer integration (method A) or by dividing computation constant by BSA before computer integration (method B).

Our results indicate that CI can be calculated directly by the thermodilution computer if the CC entered into the computer is first divided by the patient's BSA. Furthermore, we predict that CI can be calculated directly by the computer using different injectate volumes and temperatures as the CC entered into the computer controls a variable gain potentiometer that is linear for CC values recommended for clinical use in adults and children (Michael Quinn, American Edwards Laboratories, personal communication, 1981).

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Gas Scavenging Systems

To the Editor:

Accumulating evidence suggests that the risk of congenital abnormalities, spontaneous abortion, cancer, liver disease, and renal disease are increased for operating room personnel exposed to anesthetic agents (1). The Joint Commission on Accreditation of Hospitals (JCAH) addresses the potential problem in the *1981 Accreditation Manual for Hospitals*, which states, "It is recommended that each anesthesia machine be provided with a gas scavenging system" (2). This recommendation is further supported by Lecky (3) in a recent article wherein he advises operating room personnel of potential health hazards from waste anesthetic gases.

Recently, while administering anesthesia, an Ohio circle system developed alarmingly high pressure after movement of the anesthesia machine. Full opening of the circle system pop-off valve did not diminish this pressure. Subsequently, while removing the 3-L reservoir bag to relieve the increasing pressure, we discovered

compression of the corrugated evacuation tubing by the wheel of the anesthesia machine (Fig 1). Removal of this obstruction completely eliminated the pressure within the anesthesia circuit, and further ventilation proceeded without difficulty. Fortunately, the patient sustained no harm. To date, this has occurred three times during the 5 years the evacuation system has been in service.

At present, all our anesthesia machines use an Ohio evacuation system (4). Installation recommendations from Ohio advise utilization of a reducing adapter, ⅞ to ½ in. i.d. (stock no. 204-5129-731), which is connected to an Ohio relief valve with evacuator. Then, a length of ½-in. i.d. tubing (stock no. 995-6528-010) transports the gas from the relief valve. At this point, a single- or double-aspirating adapter (stock nos. 219-1365-556 or 204-5132-731) is attached. A 7½-ft reservoir tubing and ¼-in. i.d. vacuum tubing are then attached to the downstream side of the aspirating adapter. This should form a tube-within-a-tube arrangement for the entire length of the reservoir tubing. The other end of the vacuum tubing is attached to the vacuum outlet at the wall source. Even though this is the recommended assembly pattern, an evaluation of our evacuation circuits revealed that the reducing adapter (stock no. 204-5129-731) had been removed from our Ohio relief valve with evacuator. The 7½ ft corrugated tubing (stock no. 225-0834-700) had been forced over the exit from the relief valve and the corrugated tubing was allowed to carry the waste gas to floor level (Fig 2). In addition, the aspirating adapter (stock no. 219-1365-556) which is usually found 1½ ft distal to the Ohio relief valve was completely absent from the evacuation system. Furthermore, at floor level approximately 1 to 1½ ft of ¼-in. i.d. conductive vacuum tubing (stock no. 995-6436-010) were inserted into the trailing corrugated evacuation tubing leading from the relief valve (Fig 3). This was then used to conduct the waste gas to the wall outlet suction apparatus for the operating room. Further investigation of the other evacuation systems in our operating rooms revealed that this was the only circuitry used for evacuation of waste gases.

Although a similar malfunction has occurred using the Foregger gas evacuation system (5), no such report has appeared mentioning Ohio equipment. However, in this case, the situation resulted from alteration of the evacuation system either during or after installation. Yet, multiple inspections by Ohio's preventive maintenance technician did not result in notification or correction of the defective evacuation system. Whatever the cause, any system that results in a long trailing tube from the relief valve to the floor is at risk for compression by heavy objects such as an anesthesia machine. Ohio's response to this problem has not only been to send further literature regarding the appropriate assembly of this evacuation system but to develop a new evacuation system with both high-pressure and low-pressure relief devices. This system mounts above the floor and obviates any floor level tubing proxi-

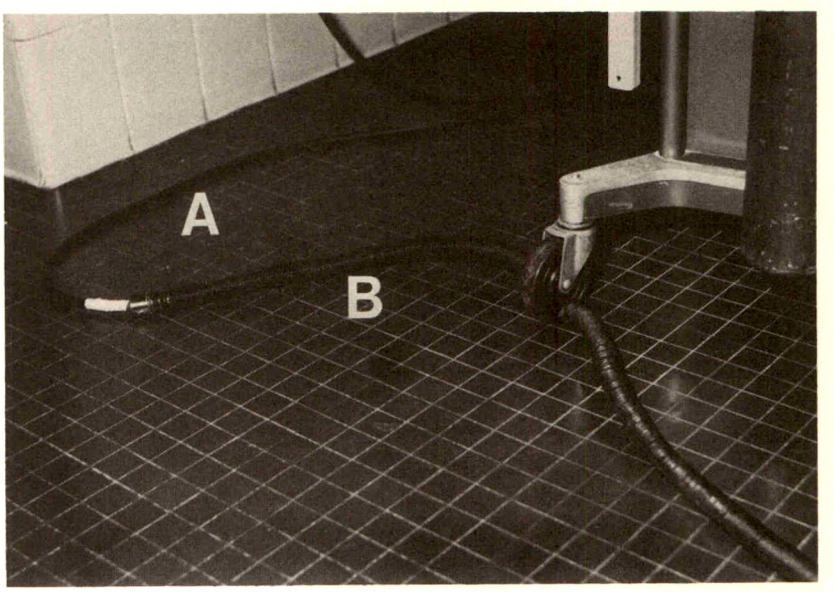


FIG 1. Corrugated tubing arising from pop-off valve is occluded by wheel of anesthesia machine.

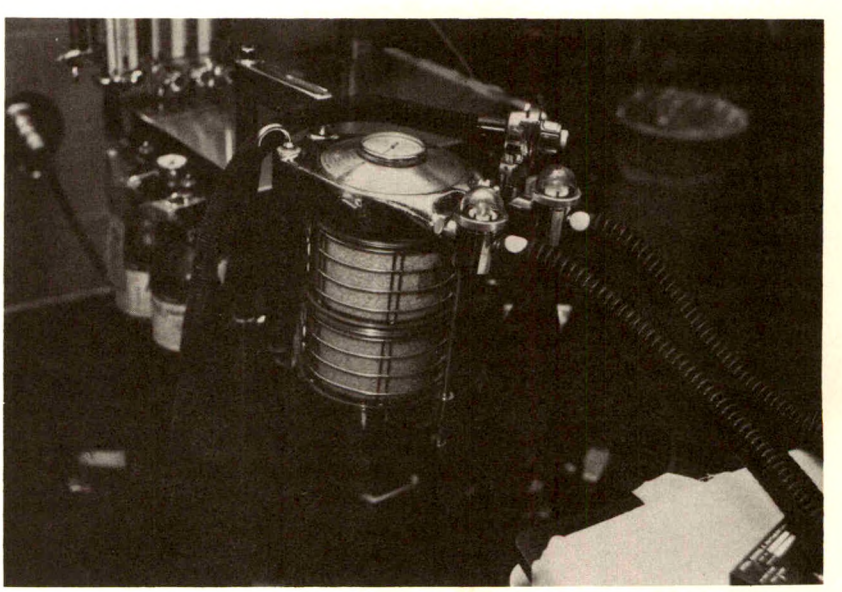


FIG 2. Corrugated conductive black reservoir tubing has been forced over exit site of Ohio relief valve.

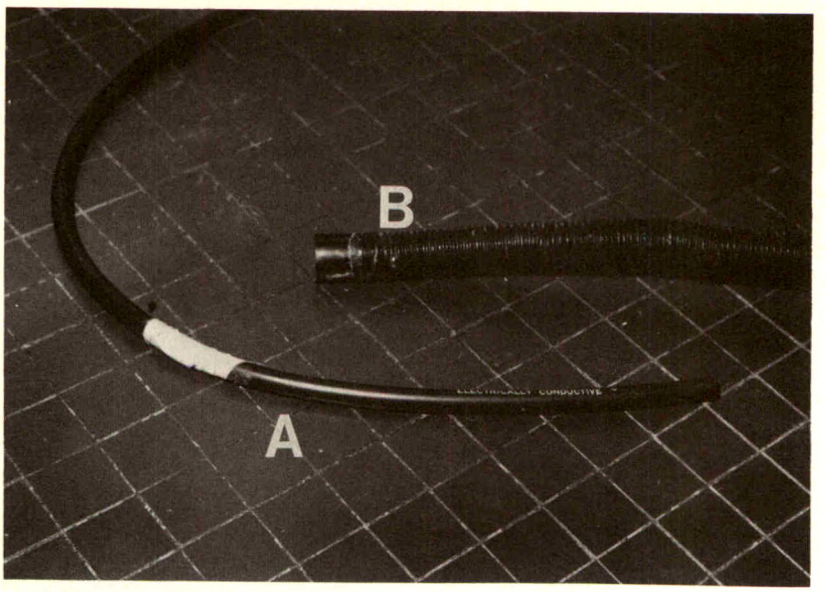


FIG 3. Smooth, electrically conductive black tubing (A) is removed from its internal placement within corrugated tubing (B) arising from pop-off valve.

mal to this safety apparatus. Since the introduction of this new evacuation system and other similar systems, we have contracted to replace our older evacuation equipment. Meanwhile, awareness of this potential hazard has eliminated any further similar complication within our department. We hope that this documentation will encourage other departments to check their evacuation systems for proper assembly and prevent further occurrences within other anesthesiology departments.

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REFERENCES

1. American Society of Anesthesiologists Ad Hoc Committee on the Effect of Trace Anesthetics on the Health of Operating Room Personnel. Occupational disease among operating room personnel: a national study. Anesthesiology 1974;41:321.
2. Joint Commission on Accreditation of Hospitals. Accreditation manual for hospitals. 1981 edition. Chicago: JCAH, 1981:9.
3. Lecky JH. Anesthetic pollution in the operating room: a notice to operating room personnel. Anesthesiology 1980;52:157–9.
4. Dorsch JA, Dorsch SE. Understanding anesthesia equipment. Baltimore: Williams & Wilkins, 1975:148.
5. Tavakoli M, Habeeb A. Two hazards of gas scavenging. Anesth Analg 1978;57:286–7.

book REVIEWS

Inherited Disease and Anaesthesia, Volume 9, edited by F. R. Ellis, Amsterdam, The Netherlands, Elsevier/North-Holland, 1981, 463 pp, $105.00.

This book is intended to review anesthetic considerations for patients with inborn errors of metabolism and heritable diseases. As the editor points out in the preface, "A reflection of the safety of modern anaesthetics is the prominence given in the medical literature to comparatively rare complications" in recent years. There are more than 100 disorders with a genetic basis. It is difficult to discuss the anesthetic implications of many of these entities because descriptions of experiences with them during surgery are based on isolated case reports. In some cases the anesthetic literature is nonexistent and recommendations regarding anesthetic care are inferred from the pathophysiology of the disorder. However, several disorders do have significant implications for the anesthesiologist and merit full and complete treatment in a monograph such as this one. These disorders include cholinesterase abnormalities, the porphyrias, malignant hyperpyrexia, several of the hemoglobinopathies, coagulation disorders, and several muscle and dermatologic diseases.

The book begins with a superficial review of the basic concepts of medical genetics and the effects of anesthetics on cell division and chromosomes. The other chapters discuss individual groups of disorders such as hereditary neurologic disorders and skeletal abnormalities; the final chapter is an overview of probability and statistics as they refer to inheritance.

The book suffers from a problem common to multiauthored texts, namely that some chapters are well written and pertinent, whereas others are of lesser quality. Also, some disorders, for example, homocystinuria, Ehlers-Danlos syndrome, and myotonia dystrophica are discussed in several different places in the book. Such fragmentation is distracting.

The information on plasma cholinesterase disorders, inborn errors of metabolism, the porphyrias, and the hemoglobinopathies is presented in a concise, readable manner. The treatment of these topics is complete. Several chapters, however, offer little and could have been either condensed or eliminated: those on mental subnormality, tissue typing, skeletal abnormalities and hereditary neurologic disorders, and cardiovascular disease. The chapters on malignant hyperpyrexia were disappointing. I question the wisdom of devoting a chapter to familial stress syndrome because, in humans, the relation between stress and malignant hyperpyrexia is controversial and poorly documented and corroborated. The inclusion of this material might give credence to as yet unproven hypotheses. To the author of the chapter, the cases are indicative of malignant hyperpyrexia but they are not based on laboratory or generally agreed upon criteria for malignant hyperpyrexia.

The chapter on malignant hyperpyrexia is adequate from the viewpoint of the clinical syndrome, but fails to present a balanced view of the current status of malignant hyperpyrexia testing. Surprisingly, there is no reference to Gronert's work and only one to Nelson's. The section on coagulation disorders lacks discussion of the clinical management of these problems. The chapter on dermatologic conditions would have benefited from color pictures and a better treatment of epidermolysis bullosa and anesthetic management of patients with this disorder. The chapter on muscle disease covers the major myopathies quite well.

The quality of the printing and the paper is high. The figures are well reproduced; however, many of them are irrelevant and do not contain accompanying descriptions.

In summary, this book, written almost exclusively by British-trained anesthesiologists and PhDs, contains some fine material, but suffers from an attempt to be too inclusive about many disorders whose significance to anesthesiologists is marginal. It fails, in some cases, to discuss the clinical management of the disorders that do have interest to the anesthesiologist. In fairness to the authors, the literature base concerning anesthetic implications of many heritable disorders is often narrow. Perhaps books such as this one will make anesthesiologists more aware and concerned about genetically determined diseases and will encourage reporting of anesthetic experience with these afflictions.

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Anesthesia, Volumes 1 and 2, edited by R. D. Miller, New York, Churchill Livingstone, 1981, 1535 pp, $98.00/set.

To date there has not been a comprehensive American reference textbook covering the field of anesthesia. Such a task would be impossible for one author, and is an enormous undertaking for multiple authors. Thus it is extremely praiseworthy that Dr.

Miller and his 31 fellow authors have collaborated to produce, for our specialty, a major new reference text. The text has an impressive list of authors. Repeatedly, they thoroughly review the literature and present referenced opinions on controversial topics. Some writers' style of writing in the first person is refreshing and helps the reader recognize sections where only opinions are being expressed. The majority of chapters in this two-volume text are well referenced with current literature. This should help overcome a chronic problem of most textbooks, namely being out of date before publication. Unlike some multiauthored texts, this work frequently utilizes internal cross references between sections when a subject is touched on more than once. Although two volumes and 1535 pages, the book retains a conciseness throughout.

Certain chapters are done extremely well. Chapter 31 (vascular surgery) is excellent and will become a standard on the subject. The chapters on hepatic and renal physiology and neuroanesthesia are equally well done. The chapter on metabolism and toxicity of inhaled anesthetics is good and easily comprehended by the nonbiochemist.

As reviewers, we naturally are led to pick details for criticism. The book contains some errors that appear to be printing errors. Most of the time these are merely an annoyance and the correct information is readily apparent. In some places, however, incorrect information is transmitted. For example, on page 803, Pa_{CO_2} is inserted in place of Pa_{O_2} which totally changes the meaning of the sentence.

There are some other surprises as well. The first chapter takes a unique and interesting approach to preoperative screening tests, but includes some assumptions. The section on monitoring seems to stress the cerebral function monitor and expensive spectral array displays over the standard 16-lead electroencephalograph. The chapter on anesthetic systems devotes a half page to the historic to-and-fro system but barely one paragraph to the practice of closed-system anesthesia. The chapter on cardiac anesthesia is poorly referenced, citing only 20 references on this vast subject.

The resident physician as well as the nurse anesthetist entering anesthesia training has long been handicapped by the lack of a comprehensive American text of anesthesia. Although journals and specialized texts will continue to lead the cutting edge in the education process, this text will be invaluable for beginners and practitioners looking for both sound background information and answers to common clinical problems.

Most of our criticism is of a minor nature. In any book there will always be details with which to argue. Overall, our feeling for the book is positive. Dr. Miller and contributors have created a reference book that its readers will appreciate. We highly recommend it to all in the practice of anesthesiology.

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Joseph M. Messick, Jr., MD
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BOOKS RECEIVED

Anesthesia and the Obese Patient: Contemporary Anesthesia Practice, Volume 5, by B. R. Brown, Philadelphia, FA Davis Co, 1981, 139 pp, $22.00.

Oxygen and Living Processes: An Interdisciplinary Approach, edited by D. L. Gilbert, Secaucus, NJ, Springer-Verlag, 1981, 401 pp, $58.50.

Brain Failure and Resuscitation, edited by A. Grenvik and P. Safar, New York, Churchill Livingstone, 1981, 268 pp, $37.50.

Chest Physiotherapy in the Intensive Care Unit, by C. F. Mackenzie, N. Ciesla, P. C. Imle, and N. Klemic, Baltimore, Williams & Wilkins Co, 1981, 260 pp, $23.00.

ANESTH ANALG
1982;61:167-223

Abstracts of Scientific Papers Presented at the 56th Congress of the International Anesthesia Research Society, San Francisco, California, March 14-18, 1982

Comparison of the Effects of Sodium Citrate and Gelusil on Gastric Acidity and Volume

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Because of the risk of acid aspiration syndrome, an oral antacid is often routinely given to parturients before induction of general anesthesia. Glycopyrrolate is also often administered before general anesthesia, to reduce gastric volume and raise gastric pH (1). Gibbs et al (2) demonstrated in dogs that particulate antacids can cause pulmonary aspiration syndrome with residual fibrosis. As a result, the use of nonparticulate antacids, especially 0.3 M sodium citrate, has gradually increased. However, reports differ as to the effectiveness of 0.3 M citrate as an antacid in vivo.

METHOD: We studied 33 patients undergoing cesarean section with general anesthesia. Approval from the Committee on Human Research was obtained. Each patient gave informed consent and was randomly assigned to receive 30 ml of either sodium citrate or Gelusil by mouth plus 0.4 mg of glycopyrrolate intramuscularly at least 30 minutes before induction. All patients had a rapid sequence induction with thiopental, succinylcholine, continuous cricoid pressure, and endotracheal intubation. Anesthesia was maintained with 50% nitrous oxide, oxygen, and low dose halogenated hydrocarbon. After delivery of the infant, an orogastric tube was placed and a sample of gastric secretion was obtained. Another sample was obtained 45 minutes later. The volume and pH of each sample were determined.

RESULTS: No statistically significant differences in pH or volume occurred between the two groups of patients (Table). The analysis of acidity was derived from hydrogen ion concentrations.

CONCLUSION: Sodium citrate (0.3 M) is effective as an antacid when given orally before induction of anesthesia. However, the high incidence of a large total gastric volume in both groups of patients indicates that the usual prophylactic maneuvers (i.e., rapid induction, cricoid pressure, intubation, and awake extubation) must continue to be used.

TABLE

pH and Volume after Administration of Gelusil or Sodium Citrate

	Gelusil (n = 17)		0.3 M sodium citrate (n = 16)	
Time between medication and first sample (min)				
Mean ± SD	56 ± 16		72 ± 12	
Range	30-90		33-133	
	Sample		Sample	
	1	2	1	2
pH (units)				
Mean	3.92	3.65	4.70	3.65
Range	2.47-8.03	2.50-7.87	3.64-6.93	3.56-7.04
Volume (ml)				
Mean (± SD)	48 ± 11	37 ± 19	26 ± 8	16 ± 15
Range	3-155	3-70	5-100	5-35
Total volume				
Mean ± SD	65 ± 47		42 ± 36	
Range	12-165		10-110	

REFERENCES:
1. Baraka A, Saab M, Salem MR, Winnie AP. Control of gastric acidity by glycopyrrolate premedication in the parturient. Anesth Analg 1977;56:642.
2. Gibbs CP, Schwartz DS, Wynne JW, et al. Anesthesiology 1979;51:380.

Heart Rate following Administration of Edrophonium-Glycopyrrolate and Edrophonium-Atropine Mixtures

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Edrophonium is an effective antagonist of pancuronium with a faster onset of action than neostigmine or pyridostigmine (1). The cardiovascular response to an edrophonium-anticholinergic agent mixture has not yet been reported. This study compares the heart rate following administration of edrophonium-atropine and edrophonium-glycopyrrolate mixtures.

METHOD: Informed consent was obtained from 52 patients scheduled for abdominal surgery. All patients were A.S.A. class I or II and without significant

TABLE

Heart Rate (HR) following Administration of Edrophonium-Glycopyrrolate (EG) or Edrophonium-Atropine (EA) Mixture*

Anesthesia	Reversal mixture	n†	HR before reversal	HR (min after injection)				
				1	2	3	4	5
						beats/min		
Balanced	EG	14	69 ± 16	66 ± 14	69 ± 15	71 ± 17	72 ± 16	72 ± 15
	EA	11	72 ± 18	76 ± 18	74 ± 17	72 ± 16	71 ± 16	72 ± 16
Volatile	EG	13	77 ± 14	71 ± 15	79 ± 14	82 ± 13	81 ± 13	80 ± 14
	EA	14	74 ± 14	80 ± 19	78 ± 13	81 ± 13	83 ± 15	83 ± 16
Combined	EG	27	73 ± 15	68 ± 14	74 ± 15	76 ± 16	77 ± 15	76 ± 15
	EA	25	73 ± 15	78 ± 18‡	76 ± 15	76 ± 16	76 ± 15	78 ± 16

* Values are means ± SD.

† Number of patients in each group.

‡ $p < 0.05$ when compared with EA.

cardiovascular disorders. Premedication included meperidine, hydroxyzine or droperidol, and atropine. Anesthesia was induced with sodium pentothal, 4 mg/kg IV, and the trachea was intubated following succinylcholine, 1 to 1.5 mg/kg IV. All patients received pancuronium in doses sufficient to cause clinically adequate muscular relaxation. Twenty-five patients had balanced anesthesia consisting of N_2O 60% to 70% with intermittent doses of fentanyl, and 27 patients had a volatile inhalation anesthetic agent, enflurane 1% to 1.5% or halothane 0.5% to 1%, in N_2O 50% to 60%. At the conclusion of surgery all the patients received edrophonium, 0.5 mg/kg IV, mixed with either glycopyrrolate, 0.5 mg, or atropine, 1 mg. The ECG was monitored continuously during the reversal, and the heart rate was recorded every minute for a period of 10 minutes. The results were analyzed by Student's *t*-test, and *p* values less than 0.05 were considered statistically significant.

RESULTS: The results are shown in the Table. One minute following the injection of the edrophonium-glycopyrrolate mixture the heart rate decreased. Occasionally bradycardia as slow as 35 beats per minute occurred. The heart rate then increased by an average of 3 beats per minute above the prereversal value and remained stable for the rest of the observation period. One minute following the injection of the edrophonium-atropine mixture the heart rate increased by an average of 5 beats per minute. The heart rate then decreased by an average of 2 beats per minute and remained stable for the rest of the observation period.

DISCUSSION: Significant changes in heart rate may occur during reversal of muscle relaxants. Such changes would be minimal if the cholinergic and anticholinergic agents mixed together have a similar onset of action. Neostigmine and glycopyrrolate have a long onset whereas edrophonium and atropine have a short one. When using neostigmine for reversal, glycopyrrolate is the recommended anticholinergic agent (2). When using edrophonium, this study suggests that atropine is the anticholinergic agent of choice.

REFERENCES:

1. Ferguson A, Egerszegi P, Bevan DR. Neostigmine, pyridostigmine, and edrophonium as antagonists of pancuronium. Anesthesiology 1980;53:390–4.
2. Mirakhur RK, Dundee JW, Clarke RSJ. Glycopyrrolate-neostigmine mixture for antagonism of neuromuscular block: comparison with atropine-neostigmine mixture. Br J Anaesth 1977;49:825–9.

Intubation: Is Low Dose Fentanyl Really Effective?

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High doses of fentanyl (75 μg/kg) are widely used to block effectively the hemodynamic consequences of endotracheal intubation in patients with coronary artery disease (1). However, the lowest effective dose of fentanyl as the *sole* anesthetic agent for this purpose has not been established. Therefore, we studied hemodynamic responses, including left ventricular ejection fraction (LVEF), during endotracheal intubation in patients with coronary artery disease to determine whether a low dose of fentanyl (30 μg/kg) also preserves left ventricular performance.

METHODS: Written informed consent was obtained from each patient in accordance with a Human Investigation Committee approved protocol. Ten patients (mean age, 58 ± 3 years) undergoing elective coronary artery bypass surgery were evaluated. LVEF was measured with the computerized nuclear probe using technetium-99m-labeled red blood cells. Additional hemodynamic measurements included: heart

TABLE

Radionuclear and Hemodynamic Data*

	LVEF	HR	SBP	PCWP	CI
	%	beats/min	mm Hg		L/min/m²
Premedication	62 ± 3	56 ± 4	148 ± 7	13 ± 1	2.6 ± 0.2
Preintubation	60 ± 3	57 ± 3	143 ± 8	15 ± 1	2.7 ± 0.1
Intubation	59 ± 2	58 ± 3	150 ± 9	16 ± 1	2.7 ± 0.2
1 min	58 ± 3	58 ± 3	154 ± 9	16 ± 1	2.5 ± 0.2
3 min	60 ± 3	55 ± 3	149 ± 9	16 ± 1	2.7 ± 0.2
5 min	60 ± 3	55 ± 3	148 ± 9	15 ± 1	2.7 ± 0.2
10 min	63 ± 4	55 ± 3	138 ± 9	15 ± 1	2.6 ± 0.2

* Abbreviations used are: LVEF, left ventricular ejection fraction; HR, heart rate; SBP, systolic blood pressure; PCWP, pulmonary capillary wedge pressure; CI, cardiac index. p values were not statistically significant.

rate (HR), blood pressure (BP), right atrial pressure (RAP), pulmonary arterial pressure (PAP), pulmonary capillary wedge pressure (PCWP), and cardiac output. Simultaneous radionuclear and hemodynamic measurements were made: (*a*) after morphine-scopolamine premedication; (*b*) following induction with fentanyl (30 μg/kg) and oxygen, plus succinylcholine infusion (preintubation); (*c*) during intubation; and (*d*) at 1-minute intervals for 10 minutes. Data are expressed as means ± SEM. Statistical analysis was performed with the one-way analysis of variance ($p < 0.01$ was considered statistically significant).

RESULTS: Results are shown in the Table. LVEF and other hemodynamic function remained unchanged throughout the study. No signs of ischemia (ECG lead V_5) were seen. No patient had recall of the anesthetic procedure.

DISCUSSION: Use of a single anesthetic agent in the minimal effective dose is, today, increasingly regarded as a goal of anesthetic management of poor risk patients. Under similar experimental conditions (1), fentanyl, 30 μg/kg, as the sole anesthetic agent is as effective as fentanyl, 75 μg/kg, in blocking the adverse effects of laryngoscopy and endotracheal intubation in patients with coronary artery disease.

REFERENCE:

1. Barash PG, Tarabadkar S, Giles R, et al. Preservation of global left ventricular function during intubation in patients with ischemic heart disease. Anesthesiology (in press 1981).

Clinical Pharmacology of Atracurium (BW 33A): A New Neuromuscular Blocking Agent

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New neuromuscular blocking agents should be non-depolarizing drugs of short-intermediate duration without cumulative properties and devoid of cardiovascular effects. Atracurium (BW 33A) has been shown in animals (1) and initial human studies (2) to meet these criteria. Atracurium's short duration of action is postulated to be secondary to Hoffmann elimination, a pH- and temperature-dependent spontaneous chemical decomposition, as well as to ester hydrolysis not dependent on plasma cholinesterase. This study investigates the neuromuscular and cardiovascular effects of atracurium in patients undergoing elective surgery under nitrous oxide-narcotic-barbiturate anesthesia.

METHODS: Seventy patients, A.S.A. class I, 18 to 59 years old, having elective surgery, gave informed consent and were studied under balanced (N_2O-fentanyl-thiopental) anesthesia. The trachea was intubated under topical lidocaine, without a relaxant. Heart rate (by tachograph), radial arterial pressure, temperature, and ECG were continuously monitored. Arterial gas tensions were maintained within normal limits. Repetitive train-of-four (2 Hz for 2 seconds repeated every 10 seconds) responses of thumb adduction were recorded. After a 15-minute stable base line period, atracurium was given as a single 5-second intravenous bolus. Maximal cardiovascular and neuromuscular changes were obtained in the absence of stimulation. Recovery of twitch to 95% of control level was measured after each initial dose, after which at least 95% block was re-established and maintained with incremental doses of 0.08 mg/kg given each time the twitch recovered to 25% of control level. When necessary, residual block was antagonized with neostigmine and atropine.

RESULTS: Results are shown in the Table. The comparative 25% to 75% recovery times in 13 patients receiving at least four successive doses of atracurium

TABLE

Neuromuscular and Cardiovascular Effects of Atracurium*

Dose	Onset	Block	Recovery to 95%	MAP	HR
mg/kg	min	%	min	%	
0.06	—	4.8	—	99.0	100.0
0.10	4.4	50.9	23.2	99.7	99.2
0.20	3.1	98.9	46.0	99.1	99.1
0.30	2.6	99.2	48.0	99.0	99.3
0.40	1.7	100.0	63.5	100.0	102.2
0.50	1.7	100.0	67.6	87.4†	105.4†
0.60	1.3	100.0	75.7	79.5†	108.3†

* Abbreviations used are: MAP, mean arterial pressure; HR, heart rate. Values for standard error not shown to save space; n = 10 throughout.

† $p < 0.05$.

were 11.45 ± 0.54 minutes and 13.27 ± 0.77 minutes for initial and final doses, respectively. This is statistically significant ($p < 0.01$), but of little clinical importance.

DISCUSSION AND CONCLUSION: The ED_{95} of atracurium is approximately 0.20 mg/kg. The onset of action at this dose is at least comparable to that of the standard agents pancuronium or metocurine. Onset is greatly shortened, however, by doubling dosage (to 0.4 mg/kg), at which full paralysis is reached in less than 2 minutes without significant cardiovascular changes with 95% twitch recovery occurring within approximately 1 hour.

The shorter duration of action of atracurium vs standard non-depolarizers, its lack of cumulative effect, and its relatively faster onset at dosage suitable for tracheal intubation (0.4 mg/kg) constitute significant advantages over current agents. In addition, its unique postulated route of degradation (Hoffmann elimination) and its excellent cardiovascular profile (which appears better than that of metocurine) constitute further advantages. Thus, atracurium appears to constitute a considerable advance in clinical relaxation and seems worthy of further studies in humans.

REFERENCES:
1. Hughes R, Chappel DJ. The pharmacology of atracurium: a new competitive neuromuscular blocking agent. Br J Anaesth 1981;53:31.
2. Payne JP, Hughes R. Evaluation of atracurium in anaesthetized man. Br J Anaesth 1981;53:45.

Isoflurane versus Halothane in Ischemic Heart Disease

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Isoflurane has the advantages of changing anesthetic depth more rapidly, better compatibility with epinephrine, and less risk of organotoxicity than halothane. Previous studies (1) of isoflurane and ischemic heart disease did not make conclusions about cardiac output or collect data during surgery. This study compares the hemodynamic effects of isoflurane and halothane during anesthesia and after surgical stimulation in humans with coronary artery disease.

METHODS: We studied 20 patients, two groups of 10 patients each, who had triple-vessel coronary artery disease and were scheduled for coronary artery bypass surgery. The groups were similar with respect to patients' age, weight, sex, body surface area, and left ventricular function (ejection fraction ≥ 0.5). The average daily dose of propranolol in the group given isoflurane was 187 mg (range 40 to 320 mg) and in the group given halothane 131 mg (range 40 to 320 mg). After premedication with morphine and scopolamine while the patients breathed 100% oxygen, heart rate, systemic arterial pressure, pulmonary arterial pressure, pulmonary capillary wedge pressure, right arterial pressure, cardiac output (thermodilution), systemic and pulmonary vascular resistance, and electrocardiogram (limb leads and V_5) were recorded. Alternate patients received either isoflurane or halothane with 50% N_2O in O_2 administered by the same anesthesiologist (J.G.C.). Intubation was accomplished after 40 mg of intravenous succinylcholine. Ventilation was controlled to produce a normal Pa_{CO_2}. Measurements during anesthesia were made 10 minutes after intubation and during surgery 10 minutes after sternotomy. Data were collected during a stable hemodynamic state and end-tidal anesthetic concentration.

RESULTS: Heart rate (HR) did not change in either group (Table). Systemic arterial pressure (SBP) decreased equally in both groups after anesthesia and returned to control values after surgical stimulation. Cardiac output (CO) decreased in both groups after

TABLE
Hemodynamic Data*

	Control		Anesthesia		Surgical stimulation	
	I	H	I	H	I	H
HR (beats/min)	58 ± 3	56 ± 4	54 ± 2	54 ± 4	63 ± 4	54 ± 5
SBP (mm Hg)	149 ± 5.0	149 ± 6.6	103 ± 4.7†	117 ± 6.6†	143 ± 9.2	142 ± 9.7
PCWP (mm Hg)	15 ± 1.3	17 ± 1.3	18 ± 1.7	19 ± 1.4	21 ± 1.1	21 ± 1.7
CO (L/min)	5.8 ± 0.4	5.2 ± 0.4	4.4 ± 0.4†	3.6 ± 0.4†	4.5 ± 0.4†,‡	3.4 ± 0.2†
SVR (dyne·sec/cm^5)	1132 ± 141	1416 ± 66	1144 ± 100‡	1683 ± 186	1700 ± 160‡,§	2263 ± 203§

* Values are means ± SE. Abbreviations used are: HR, heart rate; SBP, systemic arterial pressure; PCWP, pulmonary capillary wedge pressure; CO, cardiac output; SVR, systemic vascular resistance; I, isoflurane; H, halothane.
† $p < 0.05$ compared with control value.
‡ $p < 0.05$ compared with halothane.
§ $p < 0.05$ compared with control value and intubation.

anesthesia and surgery but was reduced more after surgery in the group given halothane. Systemic vascular resistance (SVR) was lower in the isoflurane groups after anesthesia and surgery. Right atrial, pulmonary artery, and pulmonary capillary wedge pressures, pulmonary vascular resistance, and ST segments did not change. During anesthesia and surgery, the end-tidal isoflurane concentration was 0.9 vol% with 50% N_2O (1.3 MAC) and for halothane 0.7 vol% with 50% N_2O (1.4 MAC). Increased in blood pressures and heart rates 2 minutes after intubation and 2 minutes after sternotomy were similar for the two groups.

CONCLUSIONS: Our data show that cardiac output was better sustained in the group given isoflurane even though there were changes similar to those in the group given halothane in heart rate, blood pressure, and ventricular filling pressure.

REFERENCE:
1. Mallow JE, White RD, Cucchiara RF, et al. Hemodynamic effects of isoflurane and halothane in patients with coronary artery disease. Anesth Analg 1976;55:135–8.

Postoperative Pulmonary Function with Patient-Controlled Analgesia

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Upper abdominal surgery typically produces significant pulmonary dysfunction after surgery and is accompanied by a significant incidence of atelectasis and pneumonia (1). Decreased lung volume secondary to pain and muscle splinting has been identified as the principal etiologic factor in this process (1, 2). We have undertaken a study of the postoperative impairment of forced vital capacity (FVC) and peak expiratory flow (PEF) following upper abdominal surgery in patients treated with patient-controlled analgesia (PCA) and conventional [i.e., as needed (p.r.n.) intramuscular] analgesic regimens.

The study was a randomized, controlled investigation on patients undergoing gastric bypass surgery (permission granted from the Humans Investigations Committee, University of Kentucky). Anesthetic premedication, anesthesia, and postoperative antiemetic therapy were standardized. Cigarette smokers and patients with known cardiac and pulmonary disease were excluded. Morphine sulfate was the study analgesic. Patients using the PCA unit began using the device upon emergence from anesthesia and continued until the morning of the 3rd postoperative day.

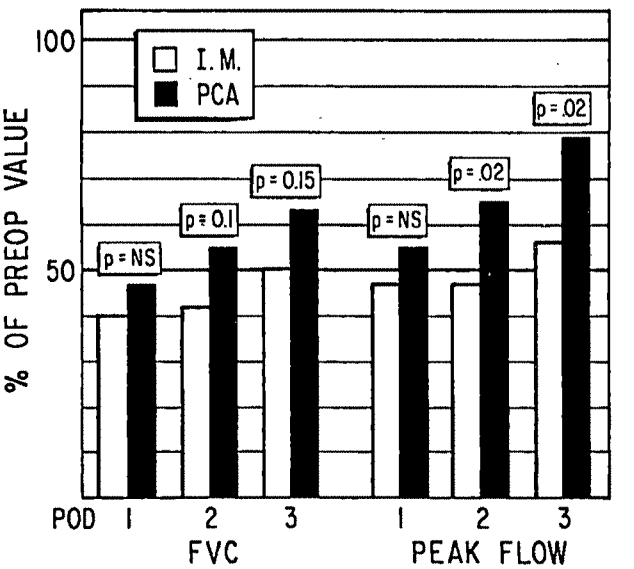


FIGURE. Pulmonary data for patients treated conventionally with intramuscular morphine (IM) and patients treated with patient-controlled analgesia (PCA) on postoperative days (POD) 1, 2, and 3.

Conventionally treated patients received morphine intramuscularly, 8 to 12 mg, every 4 to 6 hours on an as needed basis. FVC and PEF were measured before surgery, and on the 1st, 2nd, and 3rd postoperative days. Thirteen patients (six PCA treated, seven conventionally treated) were studied. Results of these measurements are seen in the Figure. Both FVC and PEF were higher for each of the three postoperative days in the PCA-treated patients. The observations are significantly different for PEF values on postoperative days 2 and 3 ($p < 0.02$); trend level significance is present for FVC on postoperative day 2 ($p < 0.1$). PCA may be a valuable tool for maintenance of the integrity of pulmonary function following abdominal surgery.

REFERENCES:
1. Craig DB. Postoperative recovery of pulmonary function. Anesth Analg 1981;60:46–52.
2. Rehder K, Marsh HM, Rodarte JR, Hyatt RE. Airway closure. Anesthesiology 1977;47:40–52.

Influence of Age on the Pharmacokinetics of Fentanyl

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A large number of studies have demonstrated that the elimination half-time of many drugs increases with increasing age. This can be due to altered clearance, volume of distribution, or both. The purpose of

this study was to compare fentanyl (F) pharmacokinetics in young adult patients (control, n = 5) and elderly (n = 4) patients undergoing elective intra-abdominal surgery.

METHODS: All patients were premedicated with diazepam (5 to 10 mg orally) and glycopyrrolate (0.2 to 0.3 mg IM). Anesthesia was induced with thiopental followed by succinylcholine to facilitate endotracheal intubation. Bolus intravenous F (10 μg/kg) was given and arterial and/or venous blood samples were collected for gas chromatographic F analysis at various intervals for 7 hours. Besides F, anesthesia was maintained with thiopental, pancuronium, and N_2O/O_2 (60:40). Individual serum concentration-time curves were subjected to weighted nonlinear least-squares regression analysis and pharmacokinetic parameters were calculated using standard equations. Statistical significance was defined as $p < 0.05$.

RESULTS: Age differed in the two groups of patients (mean: elderly patients, 67 years; control patients, 36 years) whereas weight, height, and F dose were similar. All serum concentration-time data were best described by a triexponential equation. The average terminal elimination half-time ($t_{1/2}\beta$) was longer in older patients (mean: elderly patients, 945 minutes; control patients, 265 minutes; $p < 0.01$) (Figure). The prolonged $t_{1/2}\beta$ in the elderly was entirely due to decreased clearance (mean: elderly patients, 275 ml/min; young patients, 991 ml/min; $p < 0.01$) rather than changes in volume of distribution. In this regard, linear regression revealed a correlation between age and $t_{1/2}\beta$ ($r = 0.82$, $p < 0.01$) as well as between age and clearance ($r = -0.80$, $p < 0.05$).

CONCLUSION: Serum levels of F remain high longer in older patients compared with younger patients (Figure). This results from decreasing F elimination with increasing age. This information is clinically relevant for F use in the geriatric patient population.

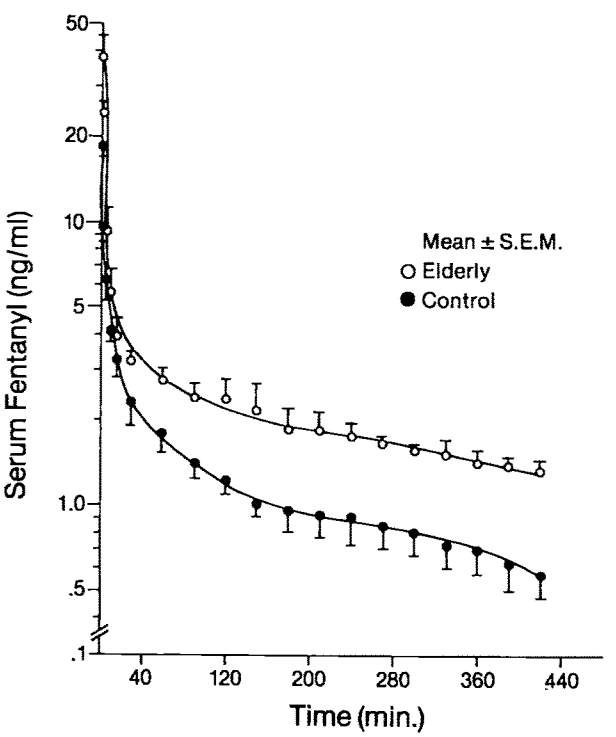


FIGURE. Serum levels of fentanyl in young adults (control) vs elderly patients.

Isoflurane-Induced and Enflurane-Induced Hepatic Necrosis in Hyperthyroid Rats

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Wood et al (1) have shown that hepatic centrilobular necrosis occurs in rats pretreated with triiodothyronine (T_3) and anesthetized with halothane 1% at normal oxygen tension (21%), but no lesion was observed in the livers from six T_3-pretreated rats anesthetized with 1.8% enflurane. We repeated these experiments using isoflurane, with the expectation that isoflurane, like enflurane, would not induce liver necrosis thus confirming that the hepatic lesion observed in hyperthyroid rats is unique to halothane anesthesia.

METHODS: Male Sprague-Dawley rats (100 to 125 g each) were given T_3, 5 mg/kg, or an alkaline saline solution, the vehicle for T_3, intraperitoneally for 6 days. On day 7, rats given T_3 were divided into three groups (five to six animals per group). Group I was anesthetized with 1.3% isoflurane and group II was anesthetized with 1% halothane, both for 2 hours in 21% oxygen (USP compressed air). Group III served as a nonanesthetized control group breathing USP compressed air for 2 hours. A fourth group which had received the vehicle for T_3 was anesthetized with 1.3% isoflurane as described for group I. The experiment was then repeated using four similar groups except that 1.8% enflurane was substituted for isoflurane. Another group of rats was pretreated with T_3 in the manner described and then received sodium pentobarbital, 40 mg/kg, intraperitoneally and breathed USP compressed air for 2 hours. All animals were killed 6 hours after the inhalational exposure. Their livers were removed, fixed, and prepared for histologic examination. Histopathologic grading of centri-

TABLE

Incidence and Severity of Hepatic Centrilobular Necrosis in Triiodothyronine-Pretreated Rats after Anesthesia

Histopathologic grade*	Isoflurane (n = 40)	Enflurane (n = 38)	Halothane (n = 89)	Pentobarbital (n = 36)	Air (n = 36)
0	20	27	7	26	36
1/2+	4	4	2		
1+	5	4	28		
2+	2	1	46		
3+	0	0	6		
4+	0	0	0		
Total incidence (%)	28	24	92	0	0

* Grades are as follows: 1/2+, necrotic cells at first cell level away from central vein and hyaline degeneration present; 1+, necrotic extruding two to three cell levels away from the central vein; 2+, necrotic cells extruding three to six cell level away from central vein; 3+, necrosis extends from one central vein to another; 4+, extensive centrilobular necrosis throughout section.

lobular necrosis on a scale of 0 to 4+ was performed by a pathologist who was unaware of the treatment received by the rats.

RESULTS: Centrilobular necrosis occurred in the livers of T_3-pretreated rats anesthetized with either isoflurane or enflurane. However, the incidence and the severity (Table) of the lesion was markedly less after isoflurane and enflurane than after halothane anesthesia. No liver necrosis occurred in pentobarbital-anesthetized T_3-pretreated rats (Table) despite the observation that the duration of anesthesia in these varied from 4.75 to 5.5 hours (interval from spontaneous loss to spontaneous return of the righting reflex), whereas recovery from 2 hours of anesthesia with the inhalational agents occurred within 20 minutes. No hepatic necrosis occurred after anesthesia in rats pretreated with the T_3 vehicle.

DISCUSSION: Liver injury by halothane is thought to be related to the biodegradation of halothane to reactive metabolite(s). Our finding that anesthesia with isoflurane and enflurane produced hepatic toxicity in T_3-pretreated rats, although at a much lower incidence and severity than with halothane anesthesia, and the relative inertness of isoflurane and enflurane suggests that, at least in T_3-pretreated rats, a mechanism other than the formation of reactive metabolites may be involved in liver toxicity. A possible mechanism is hypoxic damage to hypermetabolic liver (centrilobular) cells during anesthetic-induced depression of splanchnic blood flow.

REFERENCE:
1. Wood M, et al. Anesthesiology 1980;52:470–6.

Clonidine Increases Cardiovascular Margin of Safety for Halothane in Dogs

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Clonidine is a potent central-acting alpha-adrenergic agonist which reduces sympathetic outflow. Recently, clonidine has been reported to reduce by 48% the minimum alveolar concentration (MAC) of halothane necessary to prevent purposeful movement in response to a surgical stimulus (1). The present study was undertaken to determine whether clonidine potentiates the cardiovascular depressant effects of halothane.

METHODS: Five dogs were induced with halothane by mask, intubated under deep halothane anesthesia, and stabilized for 1 hour before starting the experimental procedure. At high (1.6 vol%) and low (0.8 vol%) halothane concentrations the following comparisons were made before and after administration of clonidine (20 μg/kg IV). (a) Heart rate (HR), mean arterial blood pressure (MAP), dP/dt (derived from left intraventricular pressure), and thermodilution cardiac output (CO) were measured by standard methods. (*b*) Levels of circulating plasma catecholamines, norepinephrine, and epinephrine were measured by high performance liquid chromatography. MAC was determined according to published methods (2) before and after administration of clonidine by varying the halothane concentration to confirm the reduction of MAC. Blood halothane levels were measured by gas chromatography.

RESULTS: MAP, dP/dt, and CO were not statistically different before and after clonidine when compared at either low or high blood halothane levels (Table). Heart rate was significantly lower after clonidine only at the low level of halothane. Control plasma norepinephrine levels were 137 ± 26 and 214 ± 8 pg/ml for high and low halothane groups, respectively, and decreased to less than 20 pg/ml after administration of clonidine at both halothane levels. Corresponding plasma epinephrine levels were 191 ± 49 and 619 ± 100 pg/ml before administration of clonidine and decreased to less than 25 pg/ml after administration of clonidine. MAC was found to be decreased by 46% 2 hours after administration of clonidine.

DISCUSSION: Administration of clonidine in doses that have been found to reduce the MAC of halothane by almost 50% produced few hemodynamic changes at either the low or high halothane level.

TABLE

Effects of Clonidine on Hemodynamic Actions of Halothane at Low and High Halothane Concentrations*

	MAP	HR	CO	dp/dt
	torr	*beats/min*	*L/min*	*torr/sec*
Low halothane				
Control values (0.8 ± 0.1 vol%)	109 ±12	100 ±4.3	2.4 ±0.5	1450 ±212
After clonidine (0.75 ± 0.2 vol%)	106 ±8.1	83† ±6.0	1.9 ±0.1	1683 ±290
High halothane				
Control values (1.6 ± 0.15 vol%)	71 ±7.7	117 ±8.0	1.8 ±0.2	867 ±104
After clonidine (1.6 ± 0.1 vol%)	65 ±9.2	109 ±5.5	1.8 ±0.4	716 ±105

* Values are means ± SEM. Abbreviations used are: MAP, mean arterial blood pressure; HR, heart rate; CO, cardiac output.

† $p < 0.05$ control values compared with values after clonidine administration.

Clonidine administration resulted in a massive reduction in sympathetic tone that was reflected by the sharp decrease in circulating plasma catecholamines, epinephrine, and norepinephrine. This reduction did not produce significant hemodynamic consequences in healthy animals. Clearly, the hemodynamics at the low halothane level (with clonidine) are less depressed than at the high halothane level (without clonidine). These data obtained at two levels of halothane imply that clonidine broadens the cardiovascular margin of safety for halothane.

REFERENCES:
1. Bloor BC, Flacke W, Randall F. Clonidine potentiation of halothane anesthesia and reversal. Anesthesiology 1980;53(3S): 13.
2. Eger EI, Saidman LJ, Brandstater B. Minimum alveolar anesthetic concentration: a standard of anesthetic potency. Anesthesiology 1965;26:756–63.

Side Effects of Epidural Morphine

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Ten healthy male volunteers (age, 18 to 33 years; weight, 62 to 120 kg), who were informed, received in random sequence 10 mg of preservative-free morphine sulfate solution either intravenously or epidurally (L2-3); they were studied during two 24-hour periods, 2 to 4 weeks apart. The study received institutional approval.

RESULTS: Blood concentrations of morphine were highest at the first sampling period (30 minutes) after both epidural or intravenous administration, and decreased exponentially below the assay sensitivity by the 6th hour. No side effects were encountered after intravenous administration of morphine, except in one subject who experienced mild nausea from the 1st to the 5th hour. All subjects were able to ambulate freely and to engage in intellectual tasks. Epidural administration of morphine resulted in more physical and mental sluggishness in all subjects after the 3rd hour and all subjects experienced one or more side effects. Generalized pruritus occurred punctually at 3.0 ± 0.33 hours (mean ± 1 SD) in nine subjects and lasted for 5.5 ± 4 hours. Six subjects had nausea at 4.1 ± 1.5 hours; it lasted for 3 ± 2.5 hours. Mild vomiting occurred in five subjects at 6.3 ± 2 hours. All subjects had some degree of urinary dysfunction following epidural morphine. In three subjects it became necessary to reverse the effects of morphine with naloxone to avoid overdistension of the bladder, in order to achieve spontaneous micturition, after bethanecol (5 mg SC) had failed to accomplish this result. All side effects were rapidly and completely reversed by naloxone.

DISCUSSION: Side effects of epidural injection are not directly related to blood concentrations of morphine. The stereotyped sequence of the complications leads us to propose that bladder dysfunction, pruritus, nausea, and vomiting may be due to a progressive modulation of somatic and visceral afferent nerve impulses caused by morphine spreading cephalad within the cerebrospinal fluid to reach brainstem structures. This is in keeping with our previous observation of rostral spread of cutaneous hypalgesia to upper cervical and trigeminal segments and with the time course of respiratory depression which peaks between 6 and 10 hours after epidural administration, as assessed by CO_2 response curves (1, 2).

REFERENCES:
1. Bromage PR, Camporesi EM, Durant PAC, Nielsen CH. Rostral spread of epidural morphine. Anesthesiology 1981;55:A149.
2. Nielsen CH, Camporesi EM, Bromage PR, Bukowski EM, Durant PAC. CO_2 sensitivity after epidural and IV morphine. Anesthesiology 1981;55:A372.

ID_{20}: Defining Myocardial Depression in Dogs

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The concept of MAC defines an anesthetic's effect on the central nervous system, but there is no such

index that defines the effect on the cardiovascular system. The end-systolic pressure-volume relationship defines the contractile state free of "contamination" from the physiologic variables of preload and afterload and has superceded pump function and ejection phase as indices of inotropy. One can use this index to define the dose of anesthetic that depresses the contractile state by 20%—or the ID_{20}.

METHODS: Twelve adult dogs were chronically instrumented to determine continuously, intracavitary pressures and dimensions by using sonomicrometry. Eight days later, dynamic ventricular volumes and pressures were determined over a wide physiologic range in the conscious state and during anesthesia with halothane and enflurane.

RESULTS: Halothane and enflurane produced a dose-dependent depression of the pressure-length relationship. The ID_{20} or dose necessary to depress the canine inotropic state by 20% was 0.63% for halothane and 1.55% for enflurane.

DISCUSSION: The extent of myocardial fiber shortening is determined by the initial fiber stretch (preload), the load resisting shortening (afterload), and the intrinsic inotropic state of the heart. As afterload increases, extent of fiber shortening decreases and end-systolic length increases. End-systolic pressure, (P_{ES}) may be linearly related to end-systolic volume (V_{ES}) by a constant (E_{ES}) which defines the inotropic state of the heart: $P_{ES} = E_{ES} (V_{ES} - V_D)$. ID_{20} for a given anesthetic may then be defined as the concentration (dose) that decreases inotropic state (E_{ES}) by 20% (Figure). These data quantify what has only been inferred previously: halothane is 2.5 times as depressive as enflurane. However, comparing ID_{20} with the respective MAC in the dog reveals that enflurane is a slightly greater cardiac depressant at equianesthetic dosage (ID_{20}/MAC = 0.63/0.87 = 0.70 for halothane; 1.55/2.2 = 0.72 for enflurane).

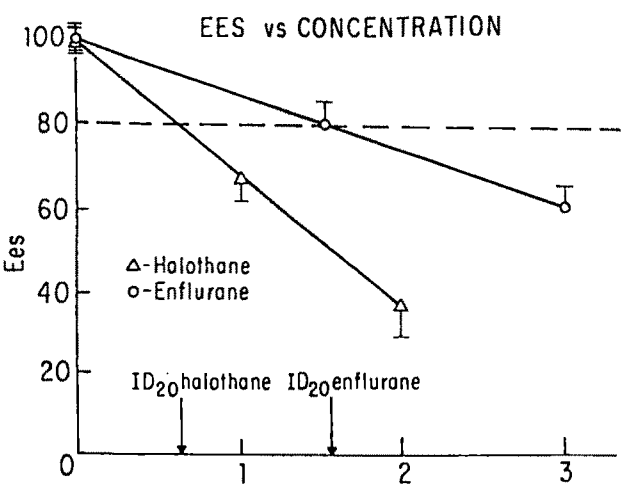


FIGURE. ID_{20} for halothane and enflurane.

REFERENCES:
1. Quasha AL, Eger EI, Tinker JH. Determinations and applications of MAC. Anesthesiology 1980;53:315–34.
2. Sagawa K. The end-systolic pressure-volume relation of the ventricle: definition, modifications and clinical use. Circulation 1981;63:1223–7.

Ventilatory Requirements during High Frequency Ventilation in Dogs

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Ventilation of anesthetized paralyzed dogs was done to determine tidal and minute volumes required to maintain the Pa_{CO_2} between 35 and 45 torr when respiratory rate (RR) was varied from 10 to 1300 breaths per minute.

METHODS: Six dogs were ventilated with either a Bird M-2 ventilator using jet ventilation with air entrainment, or with an Emerson 2-V ventilator. A modified Bennett exhalation valve placed in series with the airway allowed end-tidal analysis of CO_2 as well as Douglas bag collection and analysis of mixed expired air for CO_2 utilizing a Beckman LBI gas analyzer. Mean, peak, and minimal airway pressures

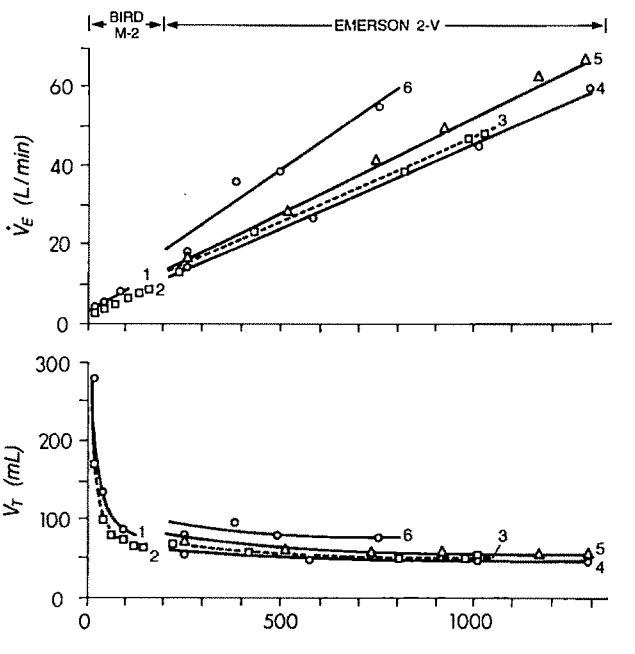


FIGURE. V_T and $\dot{V}$ required to maintain Pa_{CO_2} between 35 and 45 torr in six dogs with respiratory rates of 10 to 1300 breaths per minute.

were also measured and $\dot{V}$, V_T, and RR were determined by timed collection of expired gas in a recording water spirometer. With stepwise increases in RR, $\dot{V}$ was altered by changes in gas source pressure to maintain Pa_{CO_2} between 35 and 45 torr. Anatomical dead space was calculated from the slope of the regression line expressing the relationship between RR and $\dot{V}$ based on the Radford equation (1).

RESULTS: It was found that: (*a*) Required $\dot{V}$ increases linearly as RR increases as first established by Radford (Figure). (*b*) Required V_T decreases exponentially as rate increases and approaches a plateau at rates above 150 to 200 breaths per minute. V_T, however, always exceeded the calculated anatomical dead space. (*c*) pH, Pa_{O_2}, and Pa_{CO_2} are maintained within normal physiologic limits at rates up to 1300 breaths per minute. (*d*) Mean and peak airway pressures decreased significantly with increasing respiratory rates up to approximately 100 breaths per minute but little thereafter.

CONCLUSION: It was concluded that gas exchange during high frequency ventilation can be explained by well established concepts of ventilation and that practically no benefit accrues from respiratory rates greater than 200 breaths per minute as V_T and airway pressure cannot be significantly reduced in the face of increasing $\dot{V}$ requirements.

REFERENCE:
1. Radford EP Jr. Ventilation standards for use in artificial respiration. J Appl Physiol 1955;7:451-60.

Pharmacokinetics of Pancuronium and Org NC 45 (Norcuron)

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NC 45, a pancuronium analogue, has a duration of action significantly less than pancuronium (1). Can this difference be explained on a pharmacokinetic basis? Limitations in the sensitivity and specificity (identification of metabolites) of early assays have prevented accurate comparison of pharmacokinetic parameters of these drugs. Using a mass spectrometry assay able to distinguish metabolites from parent compound and sensitive to 150 pg/ml, we have determined the pharmacokinetics of these drugs during N_2O/halothane anesthesia in man.

METHODS: After obtaining informed consent and approval of the Human Studies Committee, nine patients were studied. Anesthesia was induced with thiopental, 2 mg/kg, and maintained with N_2O 60% and halothane 0.5% to 0.7% end-tidal, monitored by mass spectrometry. End-tidal P_{CO_2} was maintained at 35 to 40 torr, nasopharyngeal temperature was maintained at 35 to 37 C. Pancuronium or NC 45, 25 to 50 μg/kg, was administered as a 10-minute infusion. Venous blood was sampled intermittently for 8 hours and assayed for drug concentration using a mass spectrometry technique (2). Drug concentration was fitted to a two-compartment open-mamillary model using a nonlinear least-squares regression. Differences between groups were compared by unpaired Student's *t*-test ($p < 0.05$).

RESULTS: Compared with pancuronium, NC 45 had a shorter elimination half-life and higher clearance. The percentage of NC 45 recovered in the urine at 24 hours was significantly less than the percentage of pancuronium. There was no difference between drugs in distribution half-life, central compartment, or steady-state volumes (Table).

DISCUSSION: In this study, we have demonstrated that during N_2O/halothane anesthesia, the elimination half-life of NC 45 is half that of pancuronium. Thus, the shorter duration of neuromuscular blockade from NC 45 can be explained on a pharmacokinetic basis. Urinary excretion data are consistent with the observation that duration of action of NC 45 will not be prolonged in patients with renal failure.

REFERENCES:
1. Fahey MR, Morris RB, Miller RD, et al. Clinical pharmacology of ORG NC 45 (Norcuron™): a new nondepolarizing muscle relaxant. Anesthesiology 1981;55:6-11.

TABLE

Comparison of Kinetic Parameters for Pancuronium and NC 45*

	N	$t_{1/2\alpha}$	$t_{1/2\beta}$	V_1	Vd_{ss}	Clearance	Drug recovered in urine at 24 hr
		min		*L/kg*		*ml/kg/min*	%
Pancuronium	5	8.1	127	0.070	0.249	1.8	57
NC 45	4	5.6	62†	0.094	0.296	5.6†	15†

* Values shown are means. Abbreviations used are: $t_{1/2\alpha}$, distribution half-life; $t_{1/2\beta}$, elimination half-life; V_1, volume of central compartment; Vd_{ss}, volume of distribution at steady state.

† Significantly different from pancuronium.

2. Nguyen TL, Gruenke LD, Upton RA, et al: Quantitative analysis in biological fluids of the quarternary ammonium salts, pancuronium and Norcuron (ORG NC 45), by direct insertion CIMS. Biomed Mass Spec (in press 1981).

Nitroglycerin Ointment before Coronary Artery Surgery

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Estafanous and Tarazi (1) have recommended the use of nitroglycerin ointment (NTGO) before coronary artery surgery to reduce preoperative hypertension. We have studied the effects of preoperative NTGO on ST and T changes, heart rate (HR), systolic blood pressure (SP), and the rate-pressure product (RPP) in patients with coronary artery disease, from premedication until after intubation.

We studied 24 patients who were not receiving NTGO; they were 40 to 60 years old, without diabetes or hypertension in hospital, and were scheduled for elective aortal-coronary bypass surgery. Premedication was less than 4 hours before cardiopulmonary bypass and consisted of morphine sulfate, 0.15 mg/kg, scopolamine bromide, 0.05 mg/kg, in both groups and in the NTGO group approximately 0.02 in./10 kg of Nitro-bid ointment (Marion Labs). Anesthetic techniques, preoperative vital signs, ages, weights, arterial blood gas tensions, degree of coronary artery disease, and left ventricular impairment were similar in patients in both groups. ST and T changes, greater than 1 mm, were considered abnormal. The mean RPPs in the control group and the NTGO-group were analyzed by Student's *t*-test. The differences in HR, SP, and RPP between insertion of arterial line vs preintubation, "a"-line vs intubation and preintubation vs postintubation values in individual patients were also analyzed statistically using the Student's *t*-test.

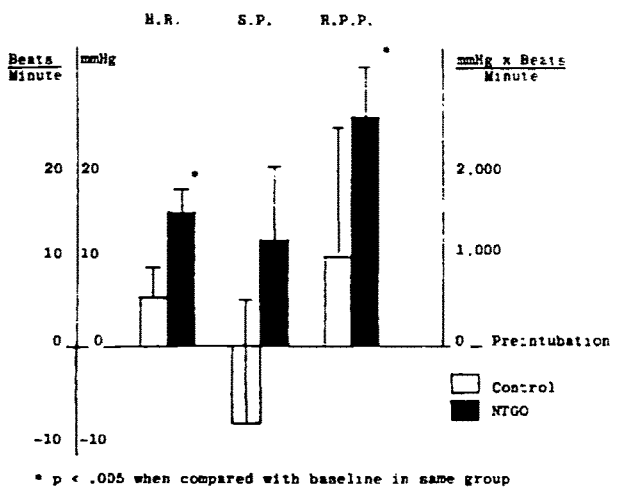


FIGURE. Differences in heart rate (HR), systolic pressure (SP), and rate-pressure product (RPP) preintubation vs postintubation. Values are means ± SE.

The mean RPPs were similar in both groups at the points studied. However, as can be seen in the Figure, the difference (preintubation vs postintubation) in mean RPP was significantly greater in the NTGO group. This is secondary to an increased HR. There was no significant change in systolic pressure.

Our dose and period of use of NTGO is within the therapeutic range. If the aim is to achieve no increase in HR, SP, or RPP preintubation and postintubation, NTGO was of no benefit and may be detrimental. This is in contrast to the findings of Armstrong et al (2) of the decrease in RPP with NTGO during acute myocardial infarction.

REFERENCES:

1. Estafanous FG, Tarazi RC. Systemic arterial hypertension associated with cardiac surgery. Am J Cardiol 1980;46:685–94.
2. Armstrong PW, Mathew MT, Boroomand K, Parker JO. Nitroglycerin ointment in acute myocardial infarction. Am J Cardiol 1976;38:474–8.

Catecholamine and Cortisol Responses to High Dose Sufentanil-O_2 and Alfentanil-O_2 Anesthesia during Coronary Artery Surgery

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High dose fentanyl-O_2 anesthesia decreases or does not change plasma catecholamine, cortisol, and antidiuretic hormone (ADH) levels in patients undergoing coronary artery bypass grafting (CABG) operations up until cardiopulmonary bypass (1). During bypass surgery, plasma catecholamine and ADH levels are usually markedly elevated and this is occasionally associated with severe hypertension. Recent studies (2) suggest that high dose alfentanil or sufentanil anesthesia may be superior to fentanyl in CABG surgery because hypertension occurs less frequently and plasma ADH levels remain unchanged throughout surgery. The effects of anesthetic doses of these two new narcotics on levels of plasma catecholamines and cortisol in patients undergoing CABG surgery have not been reported and were investigated in 30 patients in this study.

METHODS: Anesthesia was induced with sufentanil (300 μg/min IV) or alfentanil (3.0 mg/min IV) while the patients breathed oxygen. When unconscious, the patients were paralyzed with succinylcholine, intubated, and given a dose of alfentanil or

sufentanil equal to that producing unconsciousness over a 30-minute period, when surgery began. Additional sufentanil (50 μg IV) and alfentanil (2.5 to 5.0 mg IV) were given whenever systolic arterial blood pressure reached >15% above preanesthetic values. Cardiovascular dynamics were measured and blood samples for catecholamine and cortisol radioimmunoassay obtained before induction of anesthesia, when patients were unconscious, at numerous key intervals during surgery, and at the end of the operation.

RESULTS AND DISCUSSION: Cardiovascular dynamics remained remarkably stable in both groups throughout the study. The plasma cortisol level was decreased after anesthetic induction and remained decreased until the end of surgery when it returned to control values in both groups. Plasma epinephrine and norepinephrine levels remained unchanged until maximal sternal spread when they became slightly elevated. Epinephrine and norepinephrine levels were markedly increased during bypass and at the end of surgery in both groups.

These data indicate that although sufentanil and alfentanil anesthesia may be associated with more stable cardiovascular dynamics than high dose fentanyl anesthesia, catecholamine and cortisol responses during surgery are not significantly different.

REFERENCES:
1. Stanley TH, Berman L, Green O, et al. Plasma catecholamine and cortisol responses to fentanyl-oxygen anesthesia for coronary-artery operations. Anesthesiology 1980;53:250–3.
2. de Lange S, Stanley TH, Boscoe JM, et al. Antidiuretic hormone responses during coronary artery surgery with sufentanil-oxygen and alfentanil-oxygen anesthesia in man. Anesthesiology (in press 1981).

Twitch Depression and Train-of-Four Fade after Antagonism of Pancuronium with Edrophonium, Neostigmine, and Pyridostigmine

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Edrophonium, neostigmine, and pyridostigmine are clinically effective antagonists of non-depolarizing muscle relaxants. Using train-of-four stimulation they induce recovery of the first twitch height and train-of-four fade but with different time courses (1). However, if all antagonists had the same mechanism of action, then it would be expected that a given degree of recovery of the first twitch would be associated with the same degree of recovery of fade. This relationship was examined in patients receiving the same dose of relaxant.

METHODS: Thirty-six A.S.A. class I or II consenting adults scheduled for elective surgery were anesthetized with thiopental-nitrous oxide-halothane (1% to 1.5%). Neuromuscular transmission was monitored using train-of-four stimulation. Succinylcholine (1 mg/kg) was given to facilitate intubation. Following full recovery of muscle tension, pancuronium, 3 mg/70 kg, was given. When the height of the first twitch returned to 10% of control level, edrophonium, 50 or 100 mg/70 kg, neostigmine, 2.5 or 5 mg/70 kg, or pyridostigmine, 10 or 20 mg/70 kg, was given with atropine. Trains-of-four were then recorded for at least 30 minutes.

RESULTS: All patients recovered adequately, but the pattern of recovery was drug dependent. For the same twitch height, the train-of-four ratio (T_4/T_1) was greater with edrophonium than neostigmine, but smaller with pyridostigmine (Figure). The differences were statistically significant at low first twitch heights.

DISCUSSION: These differences suggest that the anticholinesterase effect of muscle relaxant antagonists is not their only mechanism of action. Furthermore, the results are compatible with quantitative differences between antagonists in their actions on presynaptic and postsynaptic receptors as described by Bowman (2). Edrophonium, would have a prefer-

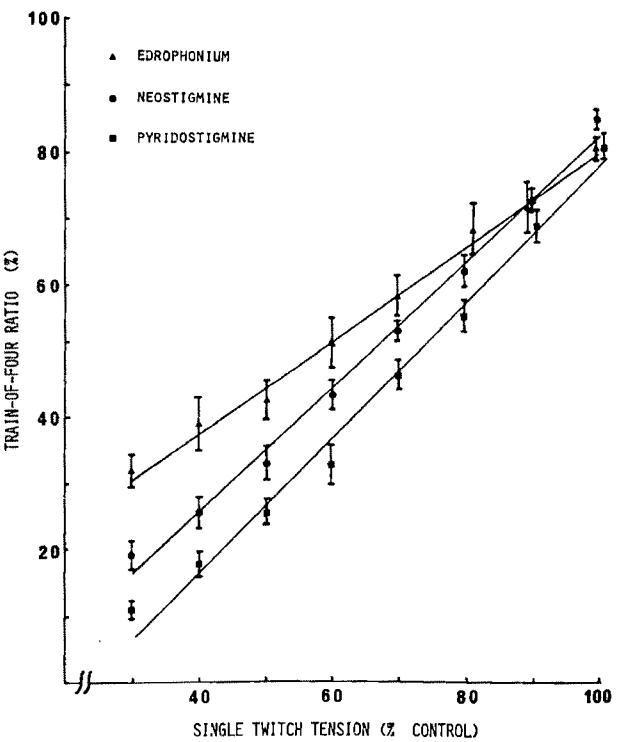


FIGURE. Train-of-four ratios for edrophonium, neostigmine, and pyridostigmine.

ential effect on the presynaptic (or fade) receptors, whereas pyridostigmine would have a more pronounced action on postsynaptic (or single twitch height) receptors.

REFERENCES:
1. Ferguson A, Egerszegi P, Bevan DR. Neostigmine, pyridostigmine, and edrophonium as antagonists of pancuronium. Anesthesiology 1980;53:390–4.
2. Bowman WC. Prejunctional and postjunctional cholinoceptors at the neuromuscular junction. Anesth Analg 1980;59:935–43.

Cerebrovascular Response to Hypoxia during Barbiturate Coma in Lambs

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The cerebrovascular response to graded hypoxia during barbiturate coma was compared with the response in the awake state.

METHOD: Cerebral blood flow, cerebral oxygen consumption, cerebral oxygen delivery, mean arterial pressure, and heart rate were obtained in awake, chronically instrumented newborn lambs at normoxia [Ca_{O_2} = 14.8 ± 0.5 vol% (mean ± SEM)] and during moderate (Ca_{O_2} = 10.6 ± 0.4 vol%) and severe (Ca_{O_2} = 7.8 ± 0.6 vol%) hypoxic hypoxia. Sufficient pentobarbital to produce electroencephalographic silence (~90 mg/kg) was then administered and the measurements repeated at normoxia (Ca_{O_2} = 14.8 ± 0.6 vol%) and at moderate (Ca_{O_2} = 11.1 ± 0.6 vol%) and severe (Ca_{O_2} = 8.1 ± 0.6 vol%) hypoxia.

In one group of animals mean arterial pressure was allowed to decrease with the induction of coma (group I), whereas in a second group pressure was maintained at its normal awake level with the use of phenylephrine (group II).

RESULTS: Mean arterial pressure did not change during hypoxia in the awake state although heart rate increased markedly in response to both moderate and severe hypoxia. When arterial pressure was not supported it decreased 37% with the induction of coma. Neither heart rate nor mean arterial pressure changed significantly when hypoxia was induced during coma.

In the awake animals cerebral blood flow increased in response to moderate hypoxia, with a further increase during severe hypoxia (Table). Cerebral metabolic rate and cerebral oxygen delivery were not altered by hypoxia.

When blood pressure was allowed to decrease during coma (group I) cerebral blood flow was reduced by 57%, cerebral metabolic rate decreased by 58%, and oxygen delivery decreased by 59%. When blood pressure was maintained (group II) cerebral blood flow decreased 37%, cerebral metabolism decreased by 44%, and oxygen delivery decreased by 37%. In neither group did hypoxia produce a significant change in cerebral oxygen consumption or oxygen delivery.

CONCLUSION: The cerebrovascular response to hypoxia remains intact during barbiturate coma in healthy lambs and flow is increased sufficiently to maintain cerebral oxygen delivery. This occurs whether or not blood pressure is supported.

Newborn and Maternal Fentanyl Levels at Cesarean Section

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Fentanyl (F) is being considered for obstetric analgesia/anesthesia because it is potent, short acting, and

TABLE

Response of Cerebral Blood Flow (CBF), Cerebral Oxygen Consumption $CMRO_2$, and Cerebral O_2 Delivery to Hypoxia with and without Blood Pressure Support*

	Normoxia (awake)	Moderate hypoxia (awake)	Severe hypoxia (awake)	Normoxia (coma)	Moderate hypoxia (coma)	Severe hypoxia (coma)
Group I (N = 8)						
MAP (mm Hg)	80 ± 4	80 ± 4	81 ± 4	50 ± 4	54 ± 4	52 ± 4
CBF (ml/100 g/min)	98 ± 9	137 ± 18	163 ± 17	42 ± 5	57 ± 12	75 ± 15
$CMRO_2$ (ml O_2/100 g/min)	6.1 ± 0.7	5.2 ± 0.3	5.7 ± 0.2	2.6 ± 0.2	2.4 ± 0.3	2.8 ± 0.3
O_2 delivery (ml O_2/100 g/min)	13.5 ± 0.7	13.1 ± 2.1	13.0 ± 1.1	5.6 ± 0.5	5.6 ± 1.1	6.6 ± 1.9
Group II (N = 8)						
MAP (mm Hg)	79 ± 3	78 ± 3	77 ± 4	79 ± 2	78 ± 3	77 ± 3
CBF (ml/100 g/min)	74 ± 3	97 ± 15	200 ± 36	47 ± 3	49 ± 3	81 ± 10
$CMRO_{O_2}$ (ml O_2/100 g/min)	4.8 ± 0.5	4.9 ± 1.0	6.4 ± 0.8	2.7 ± 0.2	2.6 ± 0.3	2.3 ± 0.6
O_2 delivery (ml O_2/100 g/min)	11.2 ± 0.6	11.2 ± 1.9	14.9 ± 0.8	7.1 ± 0.4	5.7 ± 0.5	5.7 ± 0.6

* Values are means ± SEM. MAP, Mean arterial pressure.

TABLE
Newborn–Maternal Concentration of Fentanyl

	Time (min)										
	1	2	3	4	5	6	7	8	9	10	15
	ng/ml										
Newborn	0.47	2.0	1.20	1.18	0.70	1.19	0.76	0.50	0.72	0.30	0.09
Maternal	3.03	4.70	3.24	6.63	6.19	3.08	1.93	1.51	1.98	1.09	1.59
Fetal/maternal ratio	0.15	0.43	0.44	0.18	0.11	0.38	0.39	0.33	0.37	0.28	0.06

highly protein bound. From sheep data (unpublished) maximum fetal/maternal ratio for F occurs in 5 minutes. Any effect on the fetus should be manifested by this time; therefore, neonatal evaluation is meaningful if F is given just before delivery.

METHODS: Fifteen women scheduled for elective cesarean section consented to participate in this study approved by the Human Research Committee. F (1 μg/kg) was given intravenously within 10 minutes of delivery to 11 patients under general anesthesia, and four patients under regional anesthesia. Blood samples were taken from the clamped cord and simultaneously from a second maternal vein. Blood gas analyses were done on umbilical vein samples, Apgar scores were recorded at 1 and 5 minutes, and a modified Scanlon neurobehavioral examination was performed by one investigator at 4 and 24 hours. F was analyzed by radioimmunoassay, and fetal/maternal ratios were determined for each sample point.

RESULTS: In anesthetized women, F produced no appreciable hemodynamic changes and aided the anesthetic management. The Table shows rapid peak and decline of F resembling that of pentothal. Over 10 minutes the fetal/maternal ratios averaged 0.31. Apgar scores were greater than 8, save one score of 3 at 1 minute due to obstetric difficulties. All umbilical vein Pa_{O_2} values were greater than 22 mm Hg, and neurobehavioral scores were normal at 4 and 24 hours. There were no anesthetic complications and Narcan was not required.

DISCUSSION: High lipid solubility of F would predict a rapid placental transfer; thus low fetal/maternal ratios are surprising and suggest the possibility that high protein binding of F (69%) is a factor.

Neonatal status was not impaired as determined both by our evaluations and by the nursery staff unaware of the study. The highest concentration of F in the newborn was 2 ng/ml at 2 minutes and less than 1 ng/ml after 7 minutes—barely analgesic as reported in man. This study suggests that F may be useful in human obstetrics, in particular the anesthetic management of the normal parturient during cesarean section.

One-Lung High-Frequency Positive-Pressure Ventilation during Lung Surgery

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High-frequency positive-pressure ventilation (HFPPV) (60 to 600 breaths/min) provides adequate alveolar ventilation and oxygenation at low mean and peak airway pressures with minimal untoward effects on the cardiovascular system. In intermittent positive-pressure ventilation (IPPV) during one-lung anesthesia, 21% to 65% of cardiac output may be shunted through the collapsed lung. We compared the amount of shunt during the two modalities.

METHOD: Twenty-one randomized patients undergoing one-lung thoracotomy (seven segmentactomies, 10 lobectomies, four penumonectomies) were ventilated by placement of an 8-mm i.d. single-lumen cuffed endobronchial tube in the right (10 patients) or left (11 patients) main bronchus; a straight Stortz fiberoptic bronchoscope was used for intubation. Shunt was calculated after 45 minutes of IPPV (12 breaths/min, tidal volume 10 ml/kg), and after another 45 minutes of HFPPV (150 breaths/min, driving gas pressure 20 psi, insufflation time 25%). $A\text{-}V_{O_2}$ difference was calculated from mixed venous (main pulmonary artery) samples (17 patients) or assumed as 4.5 ml (four unsampled patients). The lung was ventilated with 100% O_2 to eliminate effects of ventilation/perfusion abnormalities. The shunt was calculated using the formula $Qs/Qt = (Cc_{O_2} - Ca_{O_2})/(Cc_{O_2} - C\bar{v}_{O_2})$. Each patient served as his own control. The technique of narcotic anesthesia was standardized in all patients. The HFPPV ventilator was designed and built by the Department of Anesthesiology.

RESULTS: The calculated shunt during HFPPV compared with IPPV was significantly lower in 17 patients (81%), unchanged in two patients (9%), and slightly higher in two patients (9%). Calculated shunt during HFPPV was 5% to 30% vs 9% to 47% with IPPV.

CONCLUSIONS: HFPPV involves a lesser degree of shunt through the collapsed lung and higher Pa_{O_2} than IPPV; these result from lower airway pressure, minimal impairment to pulmonary circulation, and improved cardiac output. Hence HFPPV offers a useful alternative to IPPV during one-lung anesthesia for lung surgery.

REFERENCES:
1. Torda TA, McCulloch CH, O'Brien HD, et al. Pulmonary venous admixture during one-lung anaesthesia. Anaesthesia 1974;29:272–9.
2. Heijman G, Heijman L, Jonzon A, et al. High frequency positive-pressure ventilation during anaesthesia and routine surgery in man. Acta Anaesthesiol Scand 1972;16:176–87.

Avoidance of Carotid Artery Puncture Sequelae during Internal Jugular Cannulation

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Percutaneous cannulation of the internal jugular vein has gained widespread acceptance despite the potential complications of the technique. The right internal jugular vein (RIJ) was our first choice for this technique until a fatal complication prompted a review of our practice. In our experience over a 27-month period (January 1977 to March 1979) we had a high success rate and a remarkably constant 4% to 5% rate of carotid artery puncture: Among 1125 patients, there were 1021 attempted RIJ cannulations with 973 (95.5%) successful and 43 (4.2%) arterial punctures. When the carotid artery was punctured with a 20-gauge catheter-needle, no serious problems occurred. On five occasions, including the fatality, a #8 French introducer-sheath was inadvertently introduced into the carotid artery. We altered our routine in two ways on the basis of our review: (*a*) The external jugular vein was considered a first choice when suitable. (*b*) During RIJ cannulation, intravascular wave form and pressure were confirmed by attaching the 20-gauge catheter to a transducer before passing a guide wire and subsequent #8 French introducer-sheath.

Completion of a 27-month period (April 1979 to June 1981) of prospective analysis following this change in our routine prompts us to conclude that the alterations have made central venous cannulation safer [Among 1231 patients, there were 710 attempted RIJ cannulations (includes 542 primary attempts and 168 secondary attempts after external jugular vein failure) with 675 (95.1%) successful and 32 (4.5%) arterial punctures, and there were 659 attempted external jugular vein cannulations with 491 (74.6%) successful.]: (*a*) The overall incidence of carotid artery puncture was decreased to 2.9% because more external and fewer internal jugular punctures were attempted. However, the incidence of carotid artery puncture during RIJ cannulation did not change (4.2% vs 4.5%). (*b*) The incidence of clinically inapparent carotid artery puncture was also unchanged (5/1021 vs 4/710). However, in the latter four instances arterial puncture was confirmed when the pressure and wave form were checked via a transducer. This simple maneuver spared these four patients insertion of a #8 French introducer-sheath into the carotid artery which would have resulted in cancellation of surgery for that day and possibly significant complications.

Hemodynamic Patterns of Coronary Artery Surgery—Role of Systemic Vascular Resistance

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To determine the hemodynamic pattern underlying arterial pressure fluctuations during coronary revascularization surgery, 19 male patients with coronary artery disease were studied. None had hypertension, diabetes, major systemic disease, or severe impairment of left ventricular function.

METHODS: Mean arterial pressure (MAP), cardiac output (CO), right and left atrial pressures, hematocrit (Hct), and blood gas tensions were measured before induction of anesthesia (control) and serially until 1 hour following surgery. Systemic vascular resistance (SVR) was calculated; hemodilution to a Hct of 20 ± 2 and cold cardioplegia were used in all. Vasoactive and inotropic drugs were avoided.

RESULTS: Determinations of the hemodynamic parameters during uneventful coronary artery surgery revealed a hemodynamic pattern characteristic of different stages of surgery (Table). Following sternotomy, CO significantly decreased due to loss of negative intrathoracic pressure and decreased venous return (1). There was a reflex increase in SVR which maintained the MAP. During bypass, CO was me-

TABLE

Hemodynamic Parameters during Uneventful Coronary Artery Surgery*

	Before induction	After induction	Following sternotomy	Late in bypass	After weaning	Sternal closure	1 hr after surgery
Heart rate (beats/min)	66 ± 3.4	81 ± 3.3†‡	74 ± 3.1	—	83 ± 2.4†‡§	82 ± 5.4†	86 ± 5.8†
Systolic blood pressure (torr)	136 ± 5.9	121 ± 4.5†‡	120 ± 4.8†	—	112 ± 2.5†	116 ± 3.2†	140 ± 8.2‡§
Diastolic blood pressure (torr)	72 ± 3.2	75 ± 3.3	74 ± 2.3	—	64 ± 2.1†‡§	71 ± 3.4	83 ± 4.4‡
Mean arterial pressure (torr)	93 ± 3.7	91 ± 3.5	90 ± 2.9	55 ± 3.4†‡§	78 ± 2.0†‡§	°87 ± 3.3	100 ± 4.6‡
Right atrial pressure (torr)	9.3 ± 0.88	10.5 ± 0.77	11 ± 1.12	—	10.2 ± 1.02	9.1 ± 1.06	5.7 ± 1.35†‡§
Pulmonary capillary wedge pressure (torr)	12.1 ± 1.01	12.9 ± 1.10	13.5 ± 1.07	—	11.1 ± 0.68	10.9 ± 1.10	8.0 ± 1.3†§
Cardiac output (L/min)	4.9 ± 0.32	4.8 ± 0.32	3.9 ± 0.19†‡	4.4 ± 0.11‡§	7.0 ± 0.50†‡§	4.9 ± 0.18‡§	4.9 ± 0.39§
Systemic vascular resistance (dyne·cm·sec^{-5})	1444 ± 85	1429 ± 76	1670 ± 92†	820 ± 75†‡§	847 ± 74†§	1297 ± 102‡§	1612 ± 141
Hematocrit	41 ± 0.78	38.6 ± 0.60	37.8 ± 0.61†‡	20.5 ± 0.95†‡	22.2 ± 0.44	25.9 ± 0.93†‡§	°32.5 ± 1.64

* Values are means ± SE.
† Different from preinduction control values ($p < 0.05$).
‡ Different from previous measurement ($p < 0.05$).
§ Different from pre-bypass level ($p < 0.05$).

chanically maintained as the control; SVR and MAP were less than control values due to hemodilution and nonpulsatile flow. Immediately following bypass, CO markedly increased whereas SVR decreased due to low Hct. Low left atrial pressure indicated that cardiac performance was not depressed. Following termination of cardiopulmonary bypass, there was a gradual reduction in CO associated with gradual increase in Hct. The concomitant increase in SVR was more than can be related to the Hct changes. This suggests the interference of other mechanisms, possibly neurogenic reflexes. There was no correlation between changes in CO and MAP values, which correlated strongly with changes in SVR.

DISCUSSION: This study revealed a wide spectrum of hemodynamic patterns underlying the evolution of MAP at different stages of heart surgery. Opening the chest and alterations in Hct (1) played a dominant role in determining the level of CO, and the responses of SVR determined the level of MAP. The increased CO immediately following cardiopulmonary bypass maintained the MAP despite a low SVR. Later following cardiopulmonary bypass, while CO decreased, the gradual increase in SVR led to a steady significant increase in MAP, a hemodynamic pattern similar to that of postmyocardial revascularization hypertension. In patients with severe ventricular impairment, the hemodynamic pattern is expected to differ, as CO may not increase, and SVR changes will affect MAP more significantly (2). This study emphasizes the importance of normalizing SVR for the treatment of hypertension or hypotension.

REFERENCES:
1. Murray JF, Escobar E, Rapaport E. Effects of blood viscosity on hemodynamic responses in acute normovolemic anemia. Am J Physiol 1969;216:638–42.
2. Guyton AC, Richardson TQ. Effect of hematocrit on venous return. Circ Res 1961;9:157–64.

Hemodynamic and Catecholamine Response to Intravenous Naloxone

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Our recent observation of a catastrophic event following administration of 0.4 mg of naloxone intravenously for reversal of fentanyl (1), plus several reports (2) describing marked hemodynamic responses to intravenously administered naloxone, even with anesthetized subjects, have led us to study the effects of naloxone on the sympathetic nervous system by measuring levels of plasma epinephrine (E), norepinephrine (NE), and dopamine (DA), in patients who were without prior administration of narcotics.

MATERIALS AND METHODS: After informed consent and approval by the hospital's local committee on human research, plasma levels of E, NE, and DA were measured before and after naloxone, 0.2 mg and 0.4 mg, in six normotensive and six hypertensive surgical patients, under halothane anesthesia, and in six normotensive and five hypertensive volunteers.

Most hypertensive patients were previously receiving hydrochlorothiazide and alpha-methyldopa.

All patients were premedicated with diazepam, 0.1 mg/kg, orally 90 minutes before the scheduled operation. An intravenous induction consisted of thiopental, 4 mg/kg, followed by succinylcholine, 1.0 mg/kg, to aid orotracheal intubation. Anesthesia was maintained with halothane and 60% nitrous oxide in oxygen. Electrocardiogram, blood pressure, and nasopharyngeal temperature were monitored. A heparinized indwelling intravenous catheter and stopcock was inserted for blood sampling and measurement of plasma levels of E, NE, and DA. Control samples were obtained and naloxone, 0.2 mg, was administered. Thirty-five minutes later, samples 2 and 3 were obtained. Naloxone, 0.4 mg, was then administered and sample 4 was obtained 5 minutes later. Samples were collected in heparinized syringes and centrifuged under ice-cooled conditions. Catecholamines were assayed by radio enzymatic methods.

A heparinized catheter and two-way stopcock was inserted into a peripheral vein of the six normotensive and five hypertensive volunteers for blood sampling and for intravenous administration of naloxone. Naloxone dose and time intervals were the same except the control sample was drawn ½ hour after intravenous catheter placement.

Statistical analysis was performed using Student's *t*-test for paired data.

RESULTS: Mean arterial pressure, heart rate, and plasma levels of DA, E, and NE did not change significantly after intravenous administration of naloxone in any group of patients studied.

CONCLUSION: Our present data suggest that intravenous naloxone, without prior administration of narcotics, does not cause hemodynamic and catecholamine changes. The marked hemodynamic effects that were previously reported occurred following naloxone reversal of narcotic effects. Patients with labile hypertension have a greater blood pressure and catecholamine response to stress than do normotensive subjects. As reversal of narcotic effects is associated with sudden awakening and perception of pain, hypertensive individuals may respond with severe hypertension, cardiac arrhythmias, and pulmonary edema, as has been reported.

REFERENCES:
1. Estilo AE, Cottrell JE. Naloxone, hypertension, ruptured cerebral aneurysm. Anesthesiology 1981;54:352.
2. Patshke D, et al. Antagonism of morphine with naloxone in dogs. Anesthesiology 1977;49:525–32.

Antacid Aspiration in Rabbits

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The dangers of acid aspiration are well recognized, and administration of antacids to parturients before induction of anesthesia has been recommended in order to reduce this risk. However, aspiration of particulate antacids has been shown to cause pneumonitis (1). The present study investigated the relative potential for lung damage following aspiration of particulate and nonparticulate antacids.

METHODS: Twenty-four healthy male New Zealand White rabbits were randomly assigned to one of four groups of five rabbits each and received one of four different aspirates, or to a group of four rabbits that underwent sham aspiration. Group I received 4 ml of sterile normal saline, pH 6.5. Group II received 2 ml of Mylanta (40 mg/ml of aluminum hydroxide, 40 mg/ml magnesium hydroxide) mixed with 2 ml of pH 1.5 HCl (final pH 7.2). Group III received 4 ml of pH 1.5 HCl. Group IV received 2 ml of half-strength Bicitra (0.5 M sodium citrate, 0.3 M citric acid) plus 2 ml of pH 1.5 HCl (final pH 4.2). Group V received no aspirate. The animals were sedated with ketamine, 100 mg IM, and intubated, and the aspirate was

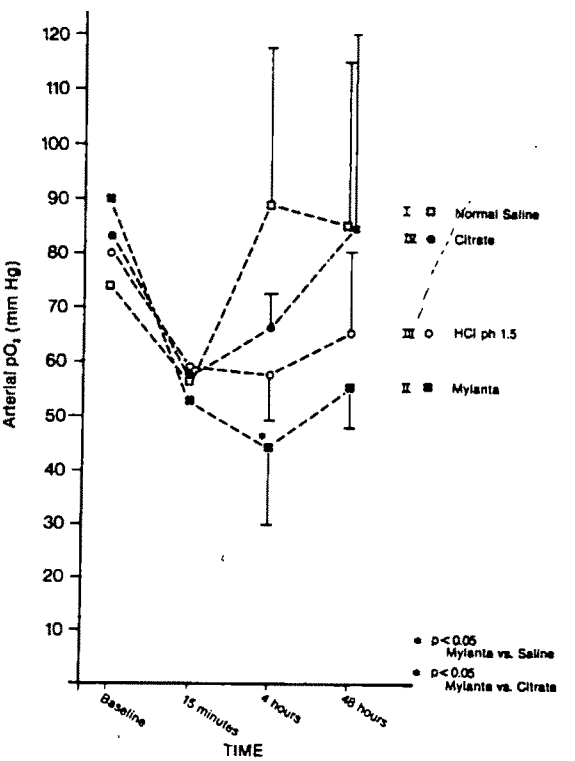


FIGURE. Arterial oxygen tension data after antacid aspiration.

TABLE

Pathology Data after Antacid Aspiration*

Group	Aspirate	Animal weight	Lung weight	Gross pathology score	Microscopic pathology score
		kg	*g*		
I	Saline	2.38 ± 0.20	16.0 ± 2.1	0 ± 0	0.2 ± 0.4
II	Mylanta	2.29 ± 0.14	23.9 ± 2.9†	3.5 ± 1.3‡	4.0 ± 0.8‡
III	HCl	2.32 ± 0.12	16.1 ± 0.5	1.2 ± 1.3	0.6 ± 0.9
IV	Bicitra	2.30 ± 0.21	14.7 ± 2.2	1.0 ± 1.0	0.8 ± 0.8
V	Sham	2.36 ± 0.20	10.5 ± 0.3§	0 ± 0	0 ± 0

* Values are means ± SE.
† $p < 0.005$ compared with all other groups.
‡ $p < 0.01$ compared with all other groups.
§ $p < 0.05$ compared with all other groups.

instilled into the lungs via a feeding tube passed through the endotracheal tube. Arterial blood was sampled before and at intervals after aspiration. The animals were killed 48 hours following aspiration and lungs were weighed and examined for gross and microscopic pathology.

RESULTS: Arterial oxygen tension data are shown in the Figure. Pa_{O_2} decreased similarly in all groups 15 minutes after aspiration, but 4 hours later it was significantly lower in the group given Mylanta than in the groups given citrate or saline. Pathology data are shown in the Table. Gross and microscopic pathology scores are defined as the number of lung lobes (of the five lobes per rabbit) showing severe consolidation on gross or microscopic examination. Lung weights and pathology scores were significantly higher in the group given Mylanta.

DISCUSSION: Pulmonary injury in rabbits following aspiration of Mylanta (a particulate antacid) is more severe than that following either aspiration of a citrate-containing (nonparticulate) antacid or aspiration of pH 1.5 HCl. This has not previously been demonstrated. Citrate is therefore preferred over Mylanta for preoperative use in situations in which the citrate antacid can be shown to be effective in neutralizing stomach contents; even omitting the antacid may be preferable to the use of Mylanta.

REFERENCE:
1. Gibbs CP, Schwartz DJ, Wynne JW, Hood CI, Kuck EJ. Antacid pulmonary aspiration in the dog. Anesthesiology 1979;51:380–5.

Nalbuphine: Hemodynamic Effects and Efficacy in Suppressing Reflex Activity in 'Balanced' Anesthesia

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The effects of morphine and nalbuphine, a new agonist-antagonist analgesic, on hemodynamics, ventilation, blood gases, and reflex suppression were compared in a double-blind, randomized study in 50 consenting patients. The groups given morphine (N = 22) and nalbuphine (N = 28) were comparable in age, sex, height, and weight. All patients underwent the same operation (total hip replacement) to standardize the surgical stimulus.

METHODS: Nalbuphine or morphine, 0.3 mg/kg, was administered 10 minutes before induction of anesthesia with thiopental. Intubation was facilitated with succinylcholine. Anesthesia was maintained with N_2O-O_2 and curare; increments of the study drug were given when signs of inadequate reflex suppression were observed. Measurements were made before, 5, and 10 minutes after study medication in the awake state; before and every 15 minutes for 1 hour after surgical incision; on emergence from anesthesia; and 1 hour after surgery.

RESULTS AND CONCLUSIONS: Significant respiratory depression occurred with both drugs before surgery. Nalbuphine was associated with hemodynamic stability, whereas hypotension occurred in six of 22 patients in the morphine group. During surgery, both drugs were effective in suppressing reflex activity. The total doses of nalbuphine and morphine were

TABLE

Postoperative Results Using Nalbuphine or Morphine

	Nalbuphine (N = 28)	Morphine (N = 22)
Narcotic reversal	0/28	14/22
Spontaneous respiration (min)	1.6 ± 0.18	9.77 ± 0.78
Spontaneous waking (min)	4.21 ± 0.6	15.09 ± 1.05
Analgesic requirements	4/28	5/22
Nausea and vomiting	0/28	14/22
Sedation	22/28	22/22

1.21 and 0.49 mg/kg, respectively. The most important postoperative results are shown in the Table.

We conclude that nalbuphine provides effective intraoperative analgesia, and its use is associated with hemodynamic stability, adequate postoperative ventilation, rapid recovery of wakefulness, few side effects, and a shorter stay in the recovery room.

Methohexital Anesthesia for Surgical Treatment of Uncontrollable Epilepsy

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Most general anesthetics, including N_2O, suppress electroencephalogram (EEG) signs of epileptiform activity, necessitating the use of "awake" techniques for intraoperative cortical mapping and focal cortical resection. The barbiturate anesthetic, methohexital, activates epileptic foci (1). We suggest that this drug is an efficacious general anesthetic for patients requiring resection of an epileptic focus. We used methohexital to anesthetize 23 patients (aged 3 to 39) with intractable seizures, and 11 patients (aged 11 to 40), who had foci delineated awake because of proximity to the speech or motor areas, served as a comparison group. All patients had their usual anticonvulsant medications tapered in preparation for surgery and their seizures were managed with paraldehyde. They were premedicated with morphine, hydroxyzine, and atropine, alone or in combination. Morphine and droperidol were titrated to produce analgesia/sedation, and anesthesia was induced with methohexital, 1.5 mg/kg, and maintained with a 0.1% drip. A non-depolarizing relaxant facilitated intubation; ventilation to P_{CO_2} 30 mm Hg was maintained with O_2/air. The scalp was infiltrated with lidocaine 0.5%, marcaine 0.375%, and epinephrine 1/200,000. A resectable abnormal EEG focus was localized in every case. All but two of the patients treated with methohexital awoke promptly in the operating room, allowing extubation and participation in neurologic assessment; none remembered the procedure. As is shown in the Figure, in the methohexital group 26% had modest improvement and 61% had substantial improvement of seizures after surgery. Seventeen percent had a significant speech or motor deficit. These results compare favorably with our awake group and with other published results (2). Thus, this technique offers surgeon and patient the benefits of general anesthesia, while allowing accurate delineation of epileptic foci.

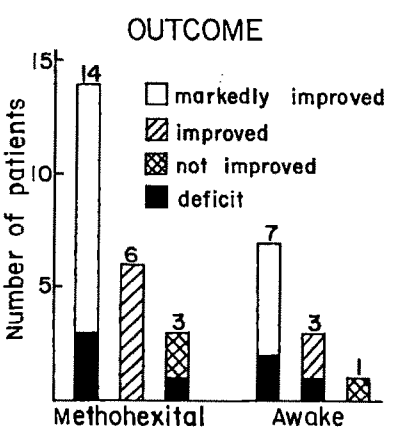


FIGURE. Effect of methohexital anesthesia on epilepsy.

REFERENCES:
1. Musella L, Wilder BJ, Schmidt RP. Electroencephalographic activation with intravenous methohexital in psychomotor epilepsy. Neurology 1971;21:594–602.
2. Rasmussen T. Cortical resection in the treatment of focal epilepsy. In: Purpura DP, Penry JK, Walter RD, eds. Neurosurgical management of the epilepsies. New York: Raven Press, 1975:139–54.

Hemodynamics during Portacaval Shunt Surgery in Humans

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Nine patients, aged 38 to 69 years with documented liver cirrhosis, complicated by portal hypertension and treated by portacaval shunting, were studied. Before anesthesia, each patient received 1.5 mg/kg of meperidine and 0.01 mg/kg of atropine sulfate intramuscularly. The anesthesia was induced with thiopental sodium (3 to 3.5 mg/kg). Muscle relaxation was achieved with pancuronium (0.1 mg/kg); anesthesia was maintained with N_2O:O_2 (F_{IO_2} = 0.35), diazepam (3 to 5 mg/hr), and fentanyl (5 to 7 μg/kg/hr). Hemodynamic variables were measured and calculated using Swan-Ganz and radial artery catheters.

Circulatory changes observed are summarized in the Table. A relatively high cardiac index before anesthesia is usually seen in patients with liver cirrhosis. Creation of portacaval shunt was associated with an increase in cardiac index and a substantial decrease in the systemic vascular resistance but no changes in heart rate and blood pressure were observed. Pulmonary artery occluded pressure increased at the opening of the shunt, reflecting increased ventricular filling. Thus, the increased venous return and the decreased peripheral resistance can be postulated as the possible causes for the increased cardiac output after portacaval shunting. Portacaval shunt allows the free passage of the portal flow into a low resistance

TABLE

Hemodynamic Data in Patients during Portacaval Shunt Surgery*

Variables‡	Stages†					
	I	II	III	IV	V	VI
HR	85 ± 4.1	87 ± 5.4	95 ± 5.2	87 ± 4.7	99 ± 3.9	106 ± 3.0
MAP	93 ± 4.9	91 ± 4.5	99 ± 3.5	92 ± 4.8	83 ± 3.6	89 ± 4.0
PAOP	15 ± 1.8	11 ± 1.2	12 ± 1.2	17 ± 1.6‖	11 ± 2.0	10 ± 2.0
CI	4.4 ± 0.5	3.8 ± 0.4§‖	4.2 ± 0.6	4.8 ± 0.5‖	4.9 ± 0.6§‖	7.2 ± 0.3§‖
LVSW	106 ± 12.5	90 ± 10.2	10815.7	103 ± 11.3	96 ± 16.0	116 ± 5.3
SVR	831 ± 100‖	1010 ± 132§	1013 ± 173§	847 ± 146‖	751 ± 109‖	566 ± 72§‖
O_2 Cons	238 ± 32‖	181 ± 22§	199 ± 26§	172 ± 27§	234 ± 45‖	261 ± 49‖
Ca_{O_2}-$C\bar{v}_{O_2}$	3.2 ± 0.3‖	2.6 ± 0.4§	2.6 ± 0.4§	1.9 ± 0.2§‖	2.9 ± 0.4	2.3 ± 0.5
Shunt	26 ± 2.5	21 ± 2.0	29 ± 3.5	28 ± 2.8	27 ± 2.7	30 ± 5.5

* Values are means ± SE.

† Stages: I, before anesthesia induction; II, after anesthesia induction, before skin incision; III, operation, before shunt formation; IV, 15 minutes after shunt formation; V, 1 hour after operation; VI, 72 hours after operation.

‡ Variables: HR, heart rate (beats/min); MAP, mean arterial pressure (torr); PAOP, pulmonary artery occluded pressure (torr); CI, cardiac index (L/min/m^2); LVSW, left ventricular stroke work (g·m/beat); SVR, systemic vascular resistance (dynes · sec · cm^{-5}); O_2 Cons, oxygen consumption (ml/min); Ca_{O_2}-$C\bar{v}_{O_2}$, arteriovenous oxygen content difference (ml O_2/100 ml of blood); Shunt, venous admixture (percentage of cardiac output).

§ $p < 0.05$ compared with stage I values according to *t*-test for paired data.

‖ $p < 0.05$ compared with stage III values according to *t*-test for paired data.

system, with an allegedly concomitant increase in arterial inflow to the preportal system, resulting in an increase in venous return and filling volumes. Patients with limited ventricular reserve and/or those given myocardial depressant doses of anesthesia could develop heart failure with the sudden increase in venous return. These data show that a balanced anesthesia technique permits the heart to compensate for the increase in venous return caused by portacaval shunt.

Somatosensory-Evoked Potential Monitoring during Neurosurgical Operations

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Sensory-evoked potentials can be used to monitor the functional integrity of sensory pathways during high risk neurosurgical operations. We monitored somatosensory cortical-evoked potentials (SCEPs) during neurosurgical operations for syringomyelia, cervical spondylosis, spinal cord tumor, arachnoid cyst, spinal cord arteriovenous malformation (AVM), chordoma of cervical spine, tethered spinal cord, and AVM of the corpus callosum. SCEP changed during surgery in eight of the 11 patients monitored. Changes cleared after intervention by the surgeon (three cases) or anesthesiologist (three cases) in every case but one. Arterial pressure was increased, retractors were moved, surgical approaches were altered, and an unstable cervical spine was repositioned. After SCEP recording during test clamping of an anterior cerebral artery, this artery, the major feeding vessel of a large AVM, was sacrificed; this patient was neurologically intact after surgery. In one case, SCEP changes were the first sign of intraoperative hypoxia. SCEP was lost on initial manipulation of an astrocytoma of the thoracolumbar cord; the lesion was not resectable, and SCEP partially recovered during closure of the wound after biopsy and dural grafting for decompression. The patient had some exacerbation of her neurologic signs immediately after surgery and recovered to her preoperative status by the 2nd postoperative day. During resection of a large spinal cord AVM, we saw progressive SCEP distortion as multiple small feeding vessels were sacrificed, and SCEP were obliterated by the conclusion of surgery. After surgery, the patient had a dense posterior column deficit and paraparesis.

SCEP monitoring during surgery correctly predicted neurologic outcome in every case. It may well have helped prevent injury in seven of our 11 patients.

Sensory-evoked potential monitoring can be a valuable adjunct to patient care during neurosurgical operations. We believe that our high success rate in obtaining technically satisfactory recordings in the operating room and in correctly predicting neurologic outcomes depends on four factors: (*a*) meticulous quality control in acquiring and processing electrophysiologic signals, (*b*) monitoring and constraint of potentially confounding pharmacologic and physiologic variables, (*c*) effective communication between

anesthesiologists and surgeons, and (*d*) quantitative representation of data in the operating room.

This work was supported in part by grant GM 27942 from the National Institute for General Medical Sciences.

Doxepin Effects on Chronic Pain, Depression, and Serum Opioids

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Depression often accompanies chronic pain, and tricyclic antidepressants are commonly prescribed in chronic pain states despite lack of documented benefit (1). In this double-blind study in patients with chronic (>6 months) low back and cervical pain and clinical depression, we compared effects of doxepin, a tricyclic antidepressant vs placebo. Purposes were to quantify "analgesic" and antidepressant effects of doxepin, and correlate mood and chronic pain perception with endogenous opioids.

METHODS: With informed consent and Human Subjects Committee approval, 14 patients with chronic pain and clinical depression (Hamilton Depression Score ≥18) were studied for six consecutive weeks. By random assignment patients received either doxepin or placebo in ascending dosage limited by either side effects or marked improvement. Dependent variables included Hamilton Depression Scores, serum beta-endorphin (New England Nuclear radioimmunoassay), serum "enkephalins" (nonspecific opioid activity by radioreceptor assay) (2), subjective ratings (0 to 100) of "pain," and "percent time pain felt," and serum levels of doxepin and desmethyl doxepin (gas chromatography-mass spectrometry). Student's *t*-test for grouped data, two-way analysis of variance, and analysis of covariance were used for data analysis. Statistical significance was set at $p < 0.05$.

RESULTS: Hamilton Depression Scores decreased significantly more for patients who received doxepin than for control patients. Enkephalins (but not beta-endorphin) increased by 68.8 ± 44.8 pmol/ml for the treatment group and decreased by 99.8 ± 44.5 pmol/ml for the control group ($p < 0.05$). After adjustments were made for between-patient variability, doxepin (39.5 ± 4.6 ng/ml) levels were significantly related to decrease in Hamilton Depression Score. Doxepin and desmethyl doxepin levels were significantly associated with a decrease in percent of time pain was felt.

CONCLUSION: Doxepin alleviates depression and pain incidence in patients with chronic low back and cervical pain. These effects may be mediated by enkephalin peptides.

This work was sponsored by Roerig, Division of Pfizer Pharmaceuticals.

REFERENCES:
1. Silverman JJ, Brennan P, Friedel RO. Clinical significance of tricyclic antidepressant plasma levels. Psychosomatics 1979;20: 736–46.
2. Naber D, Pickar D, Dionne RA, et al. Assay of endogenous opiate receptor ligands in human CSF and plasma. Substance and Alcohol Actions/Misuse 1980;1:83–91.

A Comparison of Epidural Meperidine and Bupivacaine for Relief of Labor Pain

Hammonds W, Bramwell RS, Hug CC, Najak Z, and Critz A—Emory University Hospital, Atlanta, Georgia

Epidural injection of narcotic analgesics is being used in the management of pain. We compared the analgesic efficacy of epidural meperidine with that of bupivacaine in patients in the first stage of labor. To estimate the systemic absorption of meperidine, we measured its concentrations in the plasma of mother and newborn. The neurobehavioral status of the infants was also evaluated.

METHODS: Fifteen patients in early spontaneous labor received 25 mg of meperidine through a lumbar epidural catheter. The patients graded their pain on a scale of 0 to 4. Objective ratings of pain were made on a scale of 1 to 7 based on facial expressions, bodily movements, and breathing irregularity. Pain was evaluated before and at 15, 30, 45, 60, and 120 minutes after treatment. Another 15 patients received 10 ml of 0.125% bupivacaine in the epidural space and their pain was evaluated by the same methods. These data were analyzed by the Wilcoxon rank sum test. Meperidine plasma levels were measured. Scanlon neurobehavioral assessments were obtained for infants from both groups.

RESULTS: Patients in the meperidine group had higher average pain scores than patients in the bupivacaine group in both objective and subjective ratings (Figure). At 45 and 120 minutes these differences were statistically significant ($p < 0.05$). Neurobehavioral scores for both groups were similar. No infant in either group had an inferior score although infants in both groups had borderline scores.

DISCUSSION: Epidural narcotics are said to produce pain relief without undesirable local anesthetic side effects, in doses of narcotic that have little systemic effect. When compared with bupivacaine, the

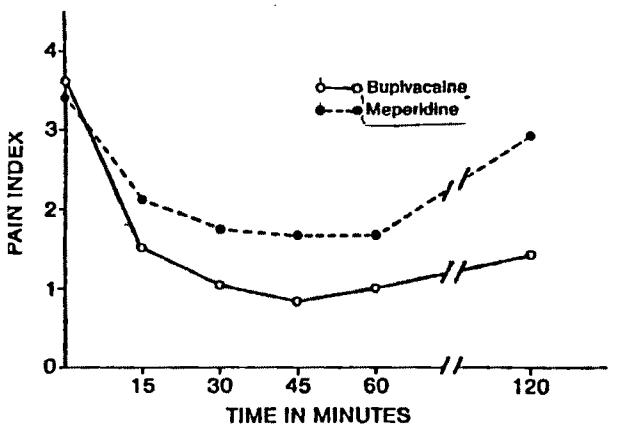


FIGURE. Subjective pain estimates. Differences are statistically significant ($p < 0.05$) at 45 and 120 minutes.

analgesia produced by epidural meperidine was variable and frequently incomplete. Although epidural meperidine may have theoretical advantages over epidural bupivacaine, these advantages were not apparent with the doses used in our patients.

Spinal Morphine Analgesia: Possible Mechanisms in Cats

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The potential importance of spinal opiate analgesia necessitates a careful evaluation of the underlying neurophysiology and pharmacology. The present study was carried out in order to determine dose-response relationships, onset, duration, and potential naloxone reversibility of spinal morphine administration.

METHODS: Cats weighing 3 to 4 kg each, were prepared for electrophysiologic recording as previously described (1). Neuronal activity of single, wide dynamic range neurons was recorded during both spontaneous activity and following the administration of a 51 C radiant heat stimulus. After control studies, the saline solution that had been bathing the spinal cord was removed and 0.3 ml of saline containing either 0.1 or 0.25 mg of morphine was applied to the spinal cord. Thirty minutes after morphine administration, naloxone, 0.2 or 0.4 mg, was applied to the spinal cord. In some instances, an additional dose of naloxone, 0.2 or 0.4 mg, was administered intravenously.

RESULTS: Spinally administered morphine, 0.25 mg, caused a significant suppression of both evoked and spontaneous activity. At 30 minutes the mean evoked activity was reduced to approximately 30% of control values, whereas the mean spontaneous activity was suppressed to 50% of control values. Morphine, 0.1 mg, caused less suppression of both types of activity. Naloxone administration caused partial reversal.

DISCUSSION: Greater suppression of evoked activity than spontaneous activity suggests that spinal morphine produces selective effects on neuronal activity associated with noxious stimulation. This correlates with human studies in which only pain is obtunded following the spinal administration of opiates. Difficulty in producing naloxone reversal is in keeping with the few reports in the literature in which reduced respiratory function following spinal opiate administration was reversed by naloxone with no reported change in analgesia. The duration of suppression correlates with the time course of spinal opiate analgesia.

This work was supported by National Institutes of Health Grant NS-09871.

REFERENCE:
1. Namiki A, Collins JG, Kitahata LM, et al. The effects of halothane on spinal neuronal response to graded noxious heat stimulation in the cat. Anesthesiology 1980;53:475–80.

Plasma Fentanyl Levels Necessary for Maintenance of Cardiovascular Stability

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To achieve and maintain autonomic stability in the open heart patient requires a nonstressful induction and continuation of suppressive anesthesia. High dose fentanyl can be used for both of these purposes. To use the rapid onset of action and the deep anesthetic properties of fentanyl correctly, some of its potential drawbacks should be considered, anticipated, and counterbalanced. Possible bradycardia and truncal rigidity can be effectively balanced by administration of a bolus of pancuronium immediately before fentanyl administration.

METHODS: Sixty patients premedicated with lorazepam underwent cardiac surgery. The patients were monitored with Swan-Ganz catheter, radial artery line, and electrocardiogram.

Induction was achieved with pancuronium, 0.1 mg/kg bolus, followed immediately by fentanyl, 50 mg/kg, given over 1 to 1.5 minutes. Intubation was preceded by laryngoscopy and intratracheal spray with lidocaine. The patients were then mechanically ven-

TABLE

Cardiovascular Measurements and Plasma Fentanyl Levels (N = 60)*

	Cardiac index	Heart rate	Systolic pressure	Systemic vascular resistance	Plasma fentanyl
	L/min/m²	*beats/min*	*torr*	*dynes/cm⁵*	*ng/ml*
Base line	2.9 ± 0.7	68 ± 0.8	147 ± 26	1400 ± 420	161 ± 72†
Postinduction	3.0 ± 0.8	76 ± 14	127 ± 24	1200 ± 430	102 ± 50
Poststernotomy	2.7 ± 0.7	71 ± 13	135 ± 20	1500 ± 450	43 ± 16

* Values are means ± SD.

† Plasma level just following infusion.

tilated. Five minutes before sternotomy, 25 mg/kg of fentanyl was administered.

Cardiovascular measurements were made before induction, 1 minute postintubation, and 1 minute poststernotomy (Table). Every fourth patient had plasma fentanyl levels drawn, 1 minute after infusion of fentanyl for induction, 3 minutes after induction when intubation was complete, and 1 minute poststernotomy.

RESULTS: The rapid induction with fentanyl did not have any adverse effects on the cardiovascular system. Total time for induction and securing endotracheal tube was 3 minutes ± 61 seconds. There was no significant change in heart rate. Twenty-two percent of the patients showed a reduction in systolic pressure on induction but none was below 100 torr; 75% were stable; and 2% increased their systolic pressure.

A decrease in systemic vascular resistance correlated with an increase in cardiac output ($r = 0.72$). No new arrythmias were detected and all of the patients were maintained at a normal end-tidal CO_2 before intubation. Changes in rate-pressure product, pulmonary wedge and central venous pressure, and pulmonary vascular resistance were not significant.

CONCLUSION: The above suggested dose regimen produces rapid induction, no cardiovascular collapse, and high enough fentanyl levels for autonomic stability in the cardiac patient.

Heparin Monitoring during Cardiopulmonary Bypass in Man: Use of Fluorogenic Heparin Assay to Validate Activated Clotting Time

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The activated clotting time (ACT) is widely used to monitor heparin levels during cardiopulmonary bypass. The ACT heparin dose-response curve method (1) for determining heparin and protamine requirements has been challenged (2). We used a heparin assay (3) which does not depend upon coagulation or protamine titration. We used it to: (*a*) determine whether ACT is a valid measure of blood heparin levels during heparin-induced anticoagulation, and (*b*) to assess the ACT heparin dose-response method of calculating protamine reversal.

METHODS: Twenty adult patients undergoing valve or coronary artery surgery gave informed consent and were randomly allocated to two groups. All received 9000 units/m^2 of porcine intestinal heparin, group I in one dose, and group II as divided doses which permitted plotting of an ACT heparin dose-response curve (1). Pump prime contained 6000 units of heparin; 1.3 mg of protamine/100 units of heparin was administered according to total heparin dose in group I, and the ACT-derived heparin dose in group II. Arterial samples were drawn at standard times for ACT and heparin determinations throughout each procedure.

RESULTS: There were no significant differences between groups with regard to overall duration of bypass (88 ± 34 minutes) and plateau hypothermia (38 ± 31 minutes). ACT and blood heparin values at four periods are presented in the Table. ACT values were significantly ($p < 0.01$) increased at hypothermia despite unchanged heparin levels. Heparin neutralization was complete in nine of 10 patients in group I

TABLE

Variation of Blood Heparin and Activated Clotting Time (ACT) with Time and Temperature (All Patients)*

Event	Heparin	ACT
	units/ml	*sec*
After 9000 units/m^2 of heparin	2.64 ± 0.21	314 ± 23.4
5 minutes on bypass	2.67 ± 0.19	441 ± 38.9
Hypothermia 20 C	2.59 ± 0.19	502 ± 40.8
Normothermia before protamine	2.44 ± 0.22	334 ± 15.2

* Values are means ± SEM.

and in seven of nine patients in group II, using the two methods of calculating protamine dosage.

DISCUSSION: Hypothermia would explain the limited heparin decay. We confirm that poor correlation exists between ACT and blood heparin (2), especially during hypothermia. Incidence of inadequate heparin reversal was not significantly increased by the smaller protamine dosage indicated by the ACT method.

We conclude that ACT is lengthened by hypothermia. Using the ACT to determine heparin needs during developing hypothermia is unreliable. The fluorogenic heparin assay, unaffected by coagulation factors, reliably detects residual heparin and offers the prospect of achieving complete heparin neutralization.

REFERENCES:
1. Bull BS, Huse WM, Bracer FS, et al. Heparin therapy during extracorporeal circulation: the use of a dose-response curve to individualize heparin and protamine dosage. J Thorac Cardiovasc Surg 1975;69:685.
2. Culliford AT, Gitel SN, Starr N, et al. Lack of correlation between activated clotting time and plasma heparin during cardiopulmonary bypass. Ann Surg 1981;193:105.
3. Mitchell GA, Gargiulo RJ, Huseby RM, et al. Assay for plasma heparin using a synthetic peptide substrate for thrombin: introduction of the fluorophore aminoisophthalic acid dimethyl ester. Thromb Res 1978;13:47.

Maternal and Neonatal Effects of Epidural Morphine for Labor

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The purpose of this study was to determine the efficacy, minimum effective dose, and potential hazards to the mother, fetus, or neonate of epidural morphine in relieving the pain of labor.

METHOD: Forty healthy parturients at term who were in active labor were studied. Human Research Committee approval and informed consent were obtained. Patients were randomly assigned to one of four groups by epidural anesthetic drug and dose: bupivacaine 0.5% (n = 10); or morphine, 2 mg (n = 9); 5 mg (n = 10); or 7.5 mg (n = 11). The volume injected through the epidural catheter was 10 ml. Neither the patient nor an evaluator knew which drug had been administered. Pain relief was assessed by both, and maternal vital signs were measured at frequent preestablished intervals, until either delivery or until the patient requested additional medication for pain. A maternal venous blood sample was obtained for blood gas analysis 6 hours after epidural injection. In all patients, correct placement of the epidural catheter was eventually confirmed by administration of a local anesthetic.

Following delivery, the condition of the newborn was assessed using Apgar scores at 1 and 5 minutes, umbilical cord gas values, and the Neurologic and Adaptive Capacity Score (1) at 2 and 24 hours of age.

RESULTS: Neither 2 mg nor 5 mg of morphine produced satisfactory analgesia. However, 7.5 mg of morphine produced satisfactory analgesia in almost two thirds of the patients. Most of these parturients had satisfactory analgesia for at least 6 hours. All of the patients requested additional analgesia for the second stage of labor. No respiratory depression or change in maternal vital signs occurred in any patient given epidural morphine. These doses of narcotics produced no detrimetnal effects on the fetus or newborn. The incidence of adverse maternal side effects was low. Pruritis occurred in three women.

CONCLUSION: We found that 2 mg and 5 mg of epidural morphine in volumes of 10 ml did not relieve the pain of labor. However, 7.5 mg of morphine in a volume of 10 ml safely relieved pain in approximately two thirds of the patients. We believe that the optimum dosage and volume of morphine injection are still to be determined. We are currently investigating the effects of a 7.5-mg dose diluted in a 20-ml volume.

REFERENCE:
1. Amiel-Tison C, et al. Anesthesiology 1980;53:S322.

Epidural Morphine for the Relief of Postoperative Pain after Cesarean Section

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The effectiveness, dose requirement, and safety of epidural morphine for relief of postoperative pain after cesarean section were studied in 40 healthy patients. Human Research Committee approval and informed consent were obtained.

METHODS: Epidural catheters were left in place following surgery until patients (four groups of 10 each) were randomly assigned to receive one of four analgesics: 2 mg, 5 mg, or 7.5 mg of epidural morphine in 10 ml of saline; or 7.5 mg of intramuscular morphine. Patients were unaware of the amount of morphine given, and the evaluator was unaware of either technique or dose. Pain relief was assessed by the patient and by the evaluator; maternal vital signs were measured at frequent preestablished intervals or until the patient requested additional medication. A mater-

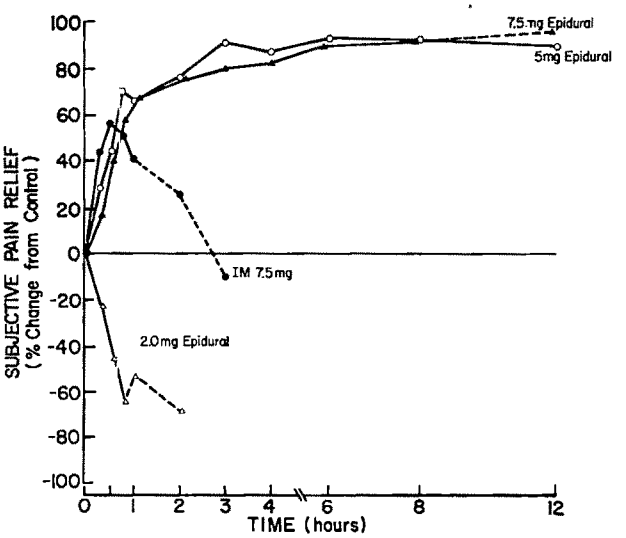


FIGURE. Postpartum cesarean section: pain relief provided by morphine.

nal venous sample was obtained for blood gas analysis just before and 6 hours after injection.

RESULTS: Our results demonstrate that 5 mg and 7.5 mg of epidural morphine give excellent pain relief having an onset of 15 to 30 minutes (Figure). The first request for additional pain medication following the 5-mg dose occurred at 29 ± 3.6 (SEM) hours. The 2-mg dose provided inadequate pain relief. The group given intramuscular morphine experienced adequate analgesia within 30 minutes, although pain relief lasted only 2 hours. Respiratory depression did not occur. Pruritis occurred frequently, but was rapidly relieved by Benadryl administration.

CONCLUSION: Doses of 5 mg and 7.5 mg of epidural morphine were highly effective in providing safe and long-lasting relief of postoperative pain after cesarean section. The 2-mg dose was inadequate.

Combined Use of Epidural Morphine and Steroid in Recurrent Postsurgical Low Back Pain Syndrome

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The variety of treatments used for controlling chronic low back pain attests to the inefficacy of current therapies. Most refractory to our multidisciplinary therapeutic approach have been patients with postsurgical relapses. Single or multiple epidural administrations of prednisolone were ineffective; morphine sulfate relieved pain in all patients, but for durations too short to be suitable for chronic pain control. For the present study, we selected 25 patients who had undergone low back surgery and whose severe recurring pain hindered their performance of normal activities. Before treatment, all of our patients underwent radiographic and computed tomographic examinations which revealed that their symptoms were associated with frequent findings of postsurgical arachnoiditis and/or intraneural scarring.

METHODS AND RESULTS: Following well established procedures, morphine (8 to 15 mg) prepared in normal saline was administered in epidural space. Prednisolone (80 to 120 mg) was administered 60 minutes later via the same route; the epidural catheter was subsequently withdrawn. Patients reported onset of pain relief within 30 minutes of morphine injection. However, a single administration of morphine and prednisolone relieved pain in all patients for more than 3 months. No motor or sympathetic blockade or postural hypotension was noticed in any of the patients. Several patients complained of severe pruritis which was promptly suppressed by intravenous naloxone (0.4 mg) without modifying the antinociceptive effects of the treatment. All of the diabetic patients experienced pruritis in a particularly severe form. Respiration was rarely depressed and only within the 1st hour. The epidural treatment was never associated with latent respiratory depression.

DISCUSSION: The combined treatment of morphine and prednisolone was beneficial to all of our patients as measured by cessation of analgesic drug intake, increased activities, and ability to resume work. Controlled clinical studies and long-term follow-up of patients will enable critical evaluation of our encouraging preliminary data.

Serum Potassium Levels during and after Ritodrine Infusion in Dogs

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Ritodrine is a beta-2-adrenergic tocolytic approved for use in premature labor. Hypokalemia has been reported with its use (1). This study determines the rate of serum potassium (K^+) decrease with ritodrine infusion and the rate of return to normal levels after discontinuing the infusion.

METHODS: Ten mongrel dogs were induced with thiopental and maintained with halothane and oxygen. Ventilation was adjusted to maintain a Pa_{CO_2} at 35 to 45 torr. Lactated Ringers' solution was infused at 5 ml/kg/hr. Ritodrine was infused at 0.0028 mg/kg/min after steady-state anesthesia. Levels of serum

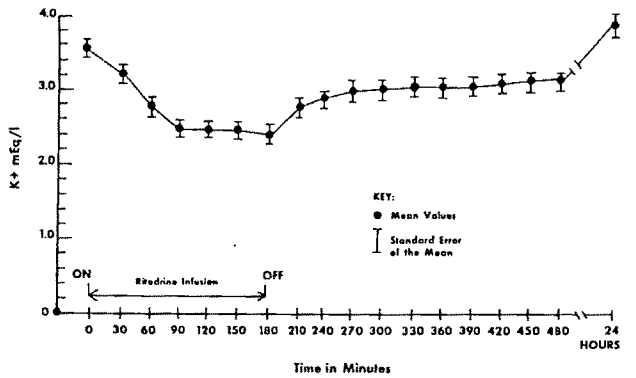


FIGURE. Serum potassium levels before, during, and after intravenous ritodrine infusion.

K^+, glucose, insulin, arterial blood gases, and urinary K^+ were sampled every 30 minutes for 3 hours. After 3 hours the ritodrine was stopped and sampling continued for 5 hours and again at 24 hours. Ten control dogs were treated identically except for infusion of ritodrine. Statistical analysis was done using the Student's *t*-test for paired data.

RESULTS: Arterial blood gas tensions remained at control levels throughout the experiment. There was no metabolic acidosis or alkalosis. Levels of serum K^+ decreased significantly ($p < 0.01$) after 30 minutes of ritodrine infusion (Figure). The levels of serum K^+ decreased for 90 minutes and then stabilized over the next 90 minutes. The levels of serum K^+ increased significantly ($p < 0.01$) after discontinuing the ritodrine infusion but did not return to preinfusion levels after 24 hours. Urinary K^+ excretion did not increase. There was no significant decrease in levels of serum K^+ in the control dogs.

DISCUSSION: Hypokalemia occurs with ritodrine as with other beta-2 drugs but the return to normal levels is much slower. This hypokalemia is probably due to a K^+ shift into the cell secondary to a glucose-insulin pump (2). The hypokalemia associated with this tocolytic agent has implications for the clinician.

REFERENCES:
1. Kaupella A, Twimala, et al: Effects of ritodrine and isoxsuprine with and without dexamethasone during late pregnancy. Obstet Gynecol 1978;51:288–92.
2. Moravec MA, Hurlbert BJ. Hypokalemia associated with terbutaline administration in obstetrical patients. Anesth Analg 1980;59:917–20.

Hydralazine for Controlled Intraoperative Hypotension

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Although sodium nitroprusside is frequently used for induction of controlled hypotension, its undesirable side effects include tachyphylaxis and possible cyanide toxicity, increased venous admixture (1), and rebound hypertension (2). Because of these and other problems we initiated a search for a better technique. This report summarizes our experience using intravenous hydralazine for controlled hypotension during neurosurgical procedures.

METHODS: The subjects were eight patients (27 to 63 years of age) undergoing craniotomy for clipping of cerebral aneurysms or arteriovenous malformations. The protocol was approved by the local Human Studies Committee. Radial arterial and thermistor-tipped pulmonary arterial catheters were placed percutaneously and control hemodynamic parameters (Table) and arterial and mixed venous blood gas tensions were determined during steady-state anesthesia [N_2O, 60% to 70% and enflurane 0.7% ± 0.2% (SE) in oxygen]. Ventilation was controlled throughout [mean Pa_{CO_2} = 29.2 ± 5.3 (SD) torr].

Arterial hypotension was induced with incremental doses of hydralazine, 5 to 10 mg IV, [mean total dose = 17 mg ± 14 (SD)] and an increase in inspired enflurane concentration to 1.1% ± 0.3% (SE). Hemodynamic parameters and arterial and mixed venous blood gas tensions were repeated when stable hypotension was achieved. Additional increments of hydralazine were given as needed to maintain hypotension and inspired enflurane concentration was held constant. Once vascular control was achieved surgically, enflurane was discontinued, blood pressure was

TABLE

Intraoperative Findings before, during, and after Hypotension*

	Before hypotension	During hypotension	After hypotension
MAP	93 ± 3.3	63 ± 2.4†	85 ± 3.8
CI	2.4 ± 0.2	2.8 ± 0.3	3.0 ± 0.4
SVR	1722 ± 135	1007 ± 114†	1344 ± 217
HR	79 ± 6.6	86 ± 5.9	83 ± 6.3
SVI	31 ± 2.4	32 ± 2.8	37 ± 3.9
SWI	35.9 ± 2.9	23.7 ± 2.2†	38 ± 4.9
PCWP	7.5 ± 0.57	7.9 ± 0.8	8.3 ± 0.7
QA/QT	14 ± 4	13 ± 2	17 ± 3
pH	7.55 ± 0.02	7.55 ± 0.01	7.55 ± 0.01

* Values are means ± SE. Abbreviations used are: MAP, mean arterial pressure (torr); CI, cardiac index ($L/min/m^2$); SVR, systemic vascular resistance (dyne · sec · cm^{-5}); HR, heart rate (beats/min); SVI, stroke volume index (ml/m^2); SWI, stroke work index ($gm \cdot m/m^2$); PCWP, pulmonary capillary wedge pressure (torr); QA/QT, venous admixture (% cardiac output).

† $p < 0.05$ vs prehypotension values.

allowed to return toward control levels, and repeat hemodynamic and blood gas data were obtained. After surgery, rebound hypertension was sought during the first hours in the intensive care unit. Data were analyzed using analysis of variance and least significant difference testing. $p < 0.05$ was regarded as statistically significant.

RESULTS: Mean time to achieve controlled hypotension was 8.7 ± 2.8 (SD) minutes and mean duration of hypotension was 27.6 minutes. Return to normotension occurred smoothly and reasonably quickly [mean time = 20.8 ± 5.7 (SD) minutes].

Intraoperative findings are summarized in the Table. Hydralazine hypotension produced a significant reduction in arterial pressure primarily by decreasing systemic vascular resistance. Unlike the effects of sodium nitroprusside we found no changes in heart rate, cardiac output, pH, or venous admixture. Cessation of controlled hypotension effectively restored hemodynamics to prehypotension values.

Rebound hypertension was not observed in any of these patients. Mean arterial pressure in the 1st hour after surgery was 97 ± 10 (SD) torr.

CONCLUSION: Our findings indicate that hydralazine, in combination with low dose enflurane anesthesia, is a smooth, rapid, predictable, reversible, and nontoxic agent for induction and maintenance of controlled hypotension. We believe this technique is valuable clinically and worthy of further investigation.

REFERENCES:

1. Benumof JL. Hypoxic pulmonary vasoconstriction and infusion of sodium nitroprusside (editorial). Anesthesiology 1979;50: 481–3.
2. Khambatta HJ, Stone JG, Khan E. Hypertension during anesthesia on discontinuation of sodium nitroprusside-induced hypotension. Anesthesiology 1979;51:127–30.

Comparison of Effects of Isoflurane versus Enflurane on Cardiovascular and Catecholamine Responses to Verapamil in Dogs

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The administration of verapamil, a slow current inhibitor, during 1 MAC halothane anesthesia resulted in decreased myocardial contractility, peripheral vascular dilation, and prolongation of AV conduction beyond the control anesthetized state (1). This study compares the effects of anesthesia with isoflurane vs enflurane on changes in cardiovascular variables and plasma catecholamine levels as a function of plasma verapamil level, to determine what differences exist in the net cardiovascular consequences and reflex response to administering verapamil during each of these anesthetics.

METHODS: Mongrel dogs, weighing 18.6 ± 1.1 (SEM) kg each, received 20 mg/kg of thiopental intravenously followed by 1 MAC isoflurane or enflurane in oxygen anesthesia. Ventilation was controlled; normothermia and normocarbia were maintained. Electrocardiogram, heart rate, mean femoral arterial blood pressure, and left ventricular dP/dt were continuously recorded. Thermodilution cardiac outputs were measured via a pulmonary artery catheter; systemic vascular resistance was calculated. Verapamil, epinephrine, and norepinephrine were measured by high performance liquid chromatography; plasma enflurane and isoflurane levels were measured by gas chromatography. After 2 hours of stabilization on isoflurane or enflurane, control measurements and plasma samples were taken. Loading doses of verapamil were followed by increasing verapamil infusion rates of 1.25, 2.5, 3.75, 5.0, etc. μg/kg/min for 30 minutes each, at which times repeat measurements and plasma samples were taken. No further verapamil was given if MAP decreased to less than 50 torr. Statistical comparison was by *t*-test.

RESULTS: Control values for isoflurane and enflurane are given in the Table; changes in cardiovascular variables and catecholamines according to plasma verapamil level are given in the Figure. Higher control values for epinephrine level, left ventricular dP/dt, and cardiac output were found for the isoflurane group. No animals in the enflurane group tolerated a plasma verapamil level greater than 525 ng/ml.

DISCUSSION: Animals receiving 1 MAC isoflurane had higher base line sympathetic tone, tolerated higher plasma verapamil levels with acceptable blood pressures, and had less resultant reflex increase in

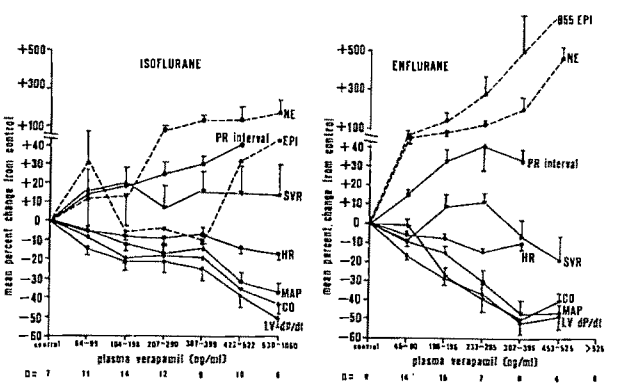


FIGURE. Changes after verapamil during 1 MAC isoflurane vs enflurane anesthesia.

TABLE

Control Values for Isoflurane and Enflurane*

	MAP	HR	LV dP/dt	CO	SVR	PR interval (ECG)	EPI	NE
	torr	*beats/min*	*torr/sec*	*L/min*	*dyne·sec/cm⁵*	*msec*	*pg/ml*	
Isoflurane (N = 7)	110 ± 6	145 ± 9	2289 ± 138†	2.53 ± 0.14†	3428 ± 332	103 ± 6	884 ± 233†	297 ± 59
Enflurane (N = 9)	98 ± 6	134 ± 6	1430 ± 40	1.85 ± 0.10	4201 ± 378	103 ± 4	303 ± 90	186 ± 24

* Values are means ± SE. Abbreviations used are: MAP, mean arterial pressure; HR, heart rate; LV dP/dt, left ventricular dP/dt; CO, cardiac output; SVR, systemic vascular resistance; EPI, epinephrine; NE, norepinephrine.

† $p < 0.05$ compared with enflurane by *t*-test.

epinephrine compared with animals given 1 MAC enflurane anesthesia. This higher degree of sympathetic tone during isoflurane anesthesia presumably protected those animals from full expression of the direct depressant effects of verapamil. Isoflurane may be a preferable inhalation agent for patients on verapamil therapy.

REFERENCE:

1. Kapur PA, Flacke WE. Verapamil-halothane: epinephrine arrhythmias and cardiovascular function. Anesthesiology 1980;53:S132.

Hemodynamic Interactions of Verapamil and Isoflurane in Dogs

Kates RA, Kaplan JA, Hug CC, Guyton R, and Dorsey LM—Emory University Hospital, Atlanta, Georgia

Verapamil is a calcium antagonist used to treat angina pectoris and dysrhythmias. As patients receiving verapamil are seen for surgery, a knowledge of its interactions with anesthetic drugs is important. We evaluated the hemodynamic interactions of verapamil and isoflurane, both myocardial depressants (1, 2).

METHODS: Eight dogs received thiopental (18 mg/kg) and succinylcholine (0.66 mg/min), and were ventilated to a normal arterial pH. Anesthesia was maintained with isoflurane (0.5 to 1.0 MAC, 0.7% to 1.4% in the oxygenator gas mixture using a Beckman LB-2 analyzer). Right heart bypass extracorporeal circulation was established. Mean aortic pressure was maintained at 100 mm Hg by appropriate flow through an aortic roller pump. Heart rate was controlled with sequential pacing. A sonomicrometer measured systolic shortening. Left ventricular function (LVF) was determined by measuring cardiac output, left atrial pressure, maximum left ventricular dP/dt, and systolic shortening. LVF studies were performed at three levels of isoflurane (0.5, 0.75, and 1.0 MAC) before and during the maintenance of stable levels of verapamil administered intravenously by bolus dose (0.2 mg/kg) and infusion (3.0 and 6.0 μg/kg/min). Verapamil concentrations were analyzed by liquid chromatography. $CaCl_2$ was administered and LVF studies repeated. Changes in LVF were analyzed by two-way analysis of variance and Student's *t*-test for paired data.

RESULTS: Isoflurane produced a concentration-dependent depression of LVF as indicated by left ventricular max dP/dt and systolic shortening at a constant left atrial pressure (10 mm Hg). This depression was enhanced in a dose-plasma concentration-dependent manner by verapamil and was partially reversed by $CaCl_2$ (Figure).

DISCUSSION: These results demonstrate that the myocardial depressant qualities of verapamil and isoflurane are additive, dose-related, and reversible by

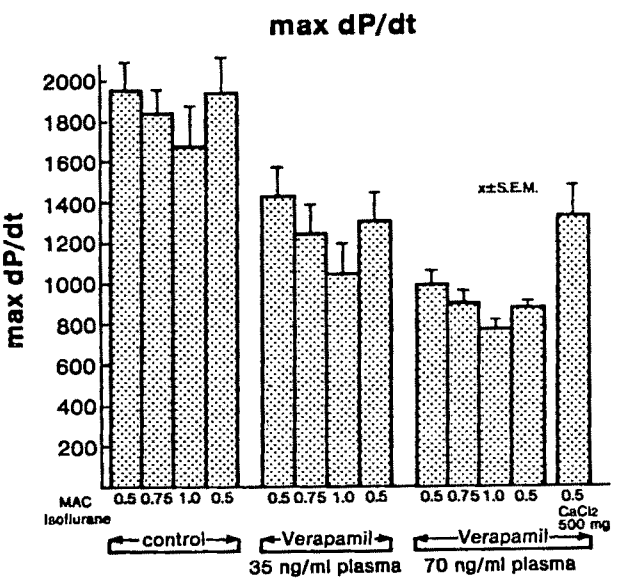


FIGURE. Depression of myocardial contractility at a constant left atrial pressure by isoflurane before and after infusion of verapamil. Two-way analysis of variance confirmed statistically significantly greater depression within each group ($p < 0.05$) and among groups ($p < 0.01$) as drug concentrations increased. Antagonism by $CaCl_2$ of depression was statistically significant ($p < 0.01$). Max dP/dt units are mm Hg·sec^{-1}. Plasma concentrations of verapamil were 35 ± 2 and 70 ± 4 ng/ml (mean ± SE).

$CaCl_2$. Extrapolation of these findings to the clinical setting must be tempered by consideration of the chronotropic and peripheral vascular effects of the drugs. However, myocardial depression from the combination of these drugs appears predictable and reversible.

REFERENCES:
1. Magnussen I, Kudsk FN. Effect of verapamil and propranolol on contractility, frequency, coronary flow and oxygen consumption in the isolated rabbit heart. Acta Pharmacol Toxicol 1974;34:141–51.
2. Kemmotsu O, Hashimoto Y, Shimosato S. Inotropic effects of isoflurane on mechanics of contraction in isolated cat papillary muscles from normal and failing hearts. Anesthesiology 1973;39:470–7.

Intravenous Labetalol in the Management of Postoperative Hypertension

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Hypertension immediately following major cardiovascular surgery has been well described (1). Increased endogenous catecholamine release and the renin-angiotensin system have been postulated as its etiology. Traditionally, treatment involves the use of drugs (i.e., sodium nitroprusside, nitroglycerine, Trimethaphen, and diazoxide), all of which may have severe side effects.

A new drug, Labetalol, is a competitive alpha- and beta-adrenergic receptor antagonist (2). Its use in the management of hypertension is well established. Its main hypotensive action relies on peripheral vascular dilation (alpha blockade), without significant reduction in cardiac output or increased pulse rate (beta blockade).

The purpose of this study was to evaluate the hemodynamic effects of Labetalol in the immediate postoperative period.

Five patients were studied over a period of 6 hours. All required antihypertensive therapy in the immediate postoperative period. Types of surgery included two coronary artery bypass grafts, two abdominal aortic artery bypass resections, and one renal artery bypass graft for renal artery stenosis. Two patients had preoperative hypertension. Each patient has a Swan-Ganz catheter inserted before surgery and had radial artery, electrocardiogram, and temperature monitors. Labetalol was administered, either by continuous intravenous infusion (2 mg/min) or by intermittent bolus injection (50 mg/3 min). Blood pressure, cardiac output, pulmonary artery pressure, mean pulmonary capillary wedge pressure, pulse rate, and urinary output were recorded. All patients were given

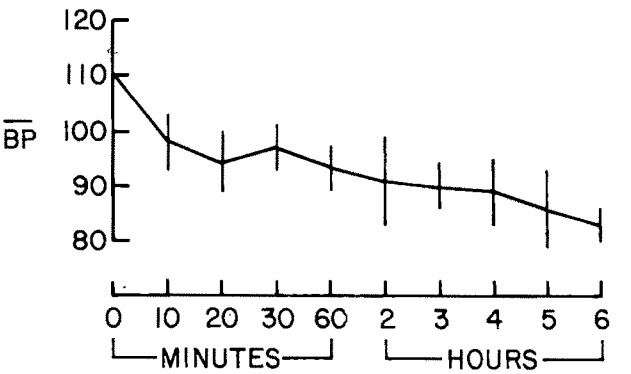


FIGURE. Effect of Labetalol on mean blood pressure.

sedation (morphine, 1 to 3 mg IV; diazepam, 1 to 3 mg IV) as required.

Labetalol reduced mean blood pressure significantly (Figure) (110 ± 5.0 mm Hg to 83 ± 2.0 mm Hg; $p < 0.05$). Both cardiac output and pulse rate variations were not statistically significant. No untoward side effects were reported.

From this preliminary study, it appears that Labetalol is an effective and safe drug for the treatment of postoperative hypertension.

REFERENCES:
1. Estafanous FG, et al. Systemic hypertension following myocardial revascularization. Am Heart J 1973;85:732.
2. Richards DA, Turner P. Proceedings of a symposium on Labetalol. Br J Clin Pharmacol 1976;3Suppl 3.

Is Jet Ventilation without Cuffed Tube Safe?

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Cuffed endotracheal tubes, especially when used for prolonged ventilation have the well known disadvantage of causing possible damage to the tracheal wall. High-frequency jet ventilation (HFJV) has shown that it can provide respiratory support without the use of cuffed tubes. But it is frequently believed that HFJV has a Venturi effect, therefore it is important to know whether the danger of aspiration is indeed increased by HFJV.

METHODS: To study this problem we performed 21 experiments on anesthetized, paralyzed dogs. The dogs were ventilated with HFJV (using IDC VS600 ventilator), and a mixture of saliva, saline, and cardiogreen was introduced into the mouth so as to form a pool. A small tracheostomy was performed at the lower trachea and an endoscope was introduced into the trachea and directed upward. This gives a good view of the vocal cords from below. Aspiration was

followed by direct observation and documented by film. In the first series of experiments, in six animals, the HFJV was administered through a 14-gauge transtracheal catheter introduced between the first and second tracheal rings. In the second series of 15 animals, two different types of translaryngeal jet catheters were introduced under direct vision. In 10 of these experiments, observations were also made under simulated cardiopulmonary resuscitation (CPR). In all experiments, frequency of ventilation and I:E ratio were varied to determine limits of safety.

RESULTS AND DISCUSSION: It was documented convincingly that aspiration does not occur under any type of HFJV under the conditions tested. This was true even if there was a head-up tilt of 10° and a fluid level up to 5 cm, provided expiration was no more than 50% of the cycle and respiratory rate 100 breaths per minute or more. If CPR was not being performed, the rate could be decreased to 60 breaths per minute and expiration prolonged to 66% without aspiration occurring. If HFJV was stopped in any of these experiments, aspiration occurred almost immediately. Starting HFJV again usually pushed the fluid back up.

CONCLUSION: We conclude that all types of HFJV currently used will prevent aspiration under most circumstances, including CPR, providing the rate and duration of expiration are appropriate. Aspirated material already in the trachea, but above the orifice of the jet catheter, will have a tendency to be expelled into the mouth. These findings have important clinical implications because they indicate that under certain circumstances it is not necessary to use a cuffed endotracheal tube.

Critical Level of Oxygen Delivery in Anesthetized Man

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Cain (1) demonstrated that the critical level of oxygen delivery, below which oxygen uptake ($\dot{V}_{O_2}$) became dependent on O_2 delivery, was 9.8 ml/kg/min in animal experiments, in which O_2 delivery was reduced by hemodilution and also by hypoxic hypoxemia. To our knowledge, such a critical level of O_2 delivery was not identified in anesthetized man. Therefore, this study examined the relationship between $\dot{V}_{O_2}$ and O_2 delivery in patients undergoing coronary artery bypass graft surgery.

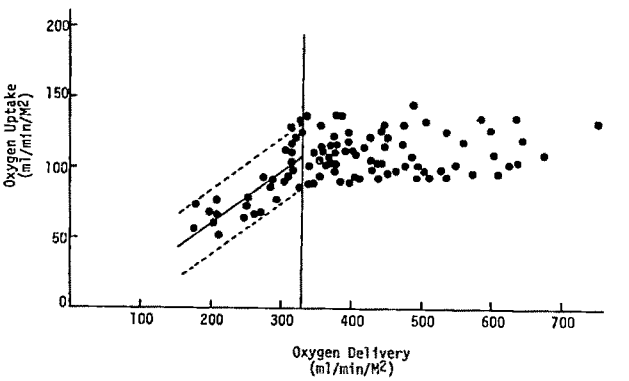


FIGURE. Relationship between oxygen delivery and oxygen uptake.

METHOD: Seventy patients were anesthetized with diazepam, pancuronium, and moderate dose of fentanyl and 99 sets of multiple hemodynamic parameters were measured after sternotomy and before cardiopulmonary bypass. $\dot{V}_{O_2}$ and oxygen delivery (cardiac output × arterial O_2 content) were calculated.

RESULT: A critical value of O_2 delivery, below which $\dot{V}_{O_2}$ became dependent on O_2 delivery was identified to be 330 ml/min/m^2 or 8.7 ml/kg/min by an analysis of the regression lines. When O_2 delivery was less than 330 ml/min/m^2, the value of $\dot{V}_{O_2}$ decreased in proportion to a decrease of O_2 delivery and $\dot{V}_{O_2}$ was expressed as follows: $\dot{V}_{O_2} = 0.36 \times O_2$ delivery $- 11.20$ ($n = 30$, $r = 0.77$, $p < 0.001$). At an O_2 delivery level greater than 330 ml/min/m^2, $\dot{V}_{O_2}$ values plateaued ($n = 69$, $r = -0.02$, $p > 0.1$) (Figure). When O_2 delivery was in the range from 180 to 330 ml/min/m^2, mixed venous P_{O_2} ($P\bar{v}_{O_2}$) was not proportional to the level of O_2 delivery and showed wide variation scattering between 31 to 44 torr. Body temperature and arterial pH during the study period were 35.1 ± 0.5 C and 7.4 ± 0.05, respectively.

DISCUSSION: Our data suggest that tissue oxygen deprivation occurs when arterial O_2 delivery is reduced to less than 330 ml/min/m^2 in anesthetized man with moderate dose of fentanyl and N_2O anesthesia. A wide variation of $P\bar{v}_{O_2}$ at O_2 delivery less than the critical level suggests that $\dot{V}_{O_2}$ was independent of $P\bar{v}_{O_2}$ when O_2 delivery was limited by the reduction of cardiac output in anesthetized patients, and under such circumstances, $P\bar{v}_{O_2}$ may not be an appropriate indicator of tissue hypoperfusion.

REFERENCE:
1. Cain SM. Oxygen delivery and uptake in dogs during anemic and hypoxic hypoxia. J Appl Physiol 1977;42:228.

Cardiovascular Effects and Gas Exchange during Isoflurane-Induced Hypotension for Cerebral Aneurysm Surgery

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Deliberate hypotension is routinely used in cerebral aneurysm surgery. No ideal hypotensive agent as yet exists that will reduce blood pressure while at the same time maintaining cardiac output and cerebral perfusion. Deep isoflurane anesthesia in human volunteers was associated with normal cardiac output despite significant decreases in systemic blood pressure (1). The purpose of this study was to determine the feasibility of using isoflurane as the maintenance anesthetic as well as the hypotensive agent and to compare the cardiovascular effects and gas exchange during induced hypotension with those in normotensive states.

METHODS: Nine patients, aged 32 to 67, were studied. All patients had suffered subarachnoid hemorrhage and were presented for cerebral aneurysm clipping. None had significant cardiovascular disease. All patients were mechanically ventilated without muscle relaxants, and maintenance anesthesia included isoflurane, nitrous oxide 66%/oxygen 34%, and small doses of fentanyl (not exceeding a total of 100 μg) administered during the initial stages of the operation. Hypotension, to a mean systemic blood pressure of 40 torr, was induced by increasing the inspired isoflurane concentration. In six subjects, a Swan-Ganz thermodilution catheter was inserted and hemodynamic variables including systemic blood pressure, pulmonary artery pressure, pulmonary wedge pressure, heart rate, and cardiac output by thermodilution were measured and recorded before, during, and after induced hypotension (Table). Arterial blood gas tensions were also obtained at each point. In addition, cerebral blood flow by intravenous xenon-133 injection was measured in three subjects.

RESULTS: The average time required to induce hypotension was 6.1 minutes and time for recovery was 5.4 minutes. Cardiac output was well maintained during the period of hypotension which varied between 20 to 120 minutes. The unchanged Pa_{O_2} and Pa_{CO_2} suggested that isoflurane-induced hypotension had no adverse effect on gas exchange. Cerebral blood flow was adequately maintained. The data confirm the previous findings in volunteers and suggest that isoflurane can be effectively used as a hypotensive agent.

REFERENCE:

1. Stevens WC, Cromwell TH, Halsey MJ, et al. The cardiovascular effects of a new inhalation anesthetic, Forane, in human volunteers at constant arterial carbon dioxide tension. Anesthesiology 1971;35:8-16.

TABLE

Comparison of Hemodynamic and Gas Exchange Data before, during, and after Isoflurane-Induced Hypotension*

	A (n = 6) Before hypotension	B (n = 6) During hypotension	C (n = 5) After hypotension
Mean inspired isoflurane concentration (%)	0.58 ± 0.04	2.28 ± 0.42† $p < 0.01$	0.53 ± 0.19 NS
Mean systemic blood pressure (mm Hg)	64.67 ± 1.80	39.50 ± 0.50† $p < 0.01$	74.40 ± 0.73 NS
Cardiac output (L/min)	5.04 ± 0.22	4.90 ± 0.31 NS	5.25 ± 0.38 NS
Heart rate (beats/min)	61.7 ± 2.56	64.3 ± 3.92 NS	67.4 ± 3.82† $p < 0.02$
Stroke volume (ml)	82.4 ± 4.89	75.8 ± 3.99 NS	77.9 ± 4.44 NS
Total vascular resistance (dyne·cm·sec^{-5})‡	810.24 ± 50.00	452.02 ± 27.43† $p < 0.01$	953.16 ± 97.51 NS
Pulmonary capillary wedge pressure (mm Hg)	13.83 ± 1.96	12.33 ± 0.62 NS	12.80 ± 1.24 NS
Pa_{O_2} (mm Hg)	112 ± 15.80	117.67 ± 17.53 NS	102.40 ± 16.54 NS
Pa_{CO_2} (mm Hg)	36.33 ± 2.36	36 ± 2.24 NS	34.2 ± 3.00 NS

* Values are means ± SEM. Statistical analyses are by Student's paired *t*-test between A-B and A-C. NS = $p > 0.05$; n = 5 in column C because hemodynamic data were not obtained in one patient due to technical difficulty.

† Differences between A-B and A-C that reach statistical significance.

‡ Total vascular resistance = mean blood pressure − pulmonary wedge pressure/cardiac output.

Comparative Cardiovascular Effects of Midazolam and Thiopental in Healthy Patients

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Midazolam, a water-soluble benzodiazepine that is shorter acting, more potent, and less irritating to veins than diazepam, induces anesthesia somewhat more slowly than thiopental, but just as smoothly. Midazolam causes less frequent apnea than thiopental but depresses respiration for a greater length of time. Inasmuch as midazolam offers an alternative to thiopental as an induction agent, the present study compares the hemodynamic effects of induction doses of midazolam with induction doses of thiopental in healthy surgical patients.

METHODS: Twenty A.S.A. class I or II male or nonpregnant female patients, aged 18 to 65, scheduled to undergo elective surgical procedures for which arterial and central venous catheters would ordinarily be placed, consented to participate in this study, as approved by the Subcommittee on Human Studies. After morphine premedication and sedation, N_2O:O_2 (4:2) was given until a stable base line of sedation and cardiovascular stability was achieved, at which point control measurements of mean arterial pressure (MAP) and mean right atrial pressure (MRAP), heart rate (HR), and cardiac output (CO), using dye dilution, were obtained. Following the base line measurement, either midazolam, 0.25 mg/kg (N = 11), or thiopental, 4 mg/kg (N = 9), randomly and blindly, was given intravenously in a bolus injection. Additional measurements of MAP, HR, MRAP, and CO were made at 2, 5, and 10 minutes after injection of the study drug. Stroke volume (SV) and systemic vascular resistance (SVR) were derived from the measured data. Each patient's measurements were compared with his own base line control values, using Student's *t*-test for paired samples; mean values for the patients given thiopental were compared with those for the patients given midazolam using Student's *t*-test for independent samples. Two-way analysis of variance was used to confirm the reported *t*-statistics and the equivalence of the starting populations for each hemodynamic measure. Differences were considered statistically significant for $p < 0.05$.

RESULTS: In the patients given thiopental, CO, MAP, HR, and SV all trended downward over the study period; MRAP increased slightly, whereas SVR remained unchanged. Significant changes from base line included the decline in CO at 5 minutes, the decrease in MAP at 2 and at 10 minutes, and the increase in MRAP at 10 minutes (Table). For patients receiving midazolam, the effects were somewhat less pronounced and less rapid in onset. Only MAP declined from base line at 2 minutes, whereas CO, HR, SV, and MRAP did not change. SVR decreased slightly at 2 minutes, paralleling the decrease in MAP. At 5 and at 10 minutes, CO, MAP, HR, and SV decreased slightly but no further changes in MRAP or in SVR were observed. The only significant changes from base line were the 5- and 10-minute decreasing of MAP. When the two groups were compared with each other, however, no significant differ-

TABLE

Cardiovascular Effects of Midazolam and Thiopental*

	CO	MAP	MRAP	HR	SVR	SV
	L/min	*mm Hg*		*beats/min*	*mm Hg/L/min*	*ml*
Midazolam						
Base line values	6.8 ± 2.7	101 ± 18	6 ± 3	85 ± 18	15 ± 5	80 ± 25
2 min	6.8 ± 2.3	89 ± 13	7 ± 3	86 ± 14	13 ± 3	80 ± 24
5 min	6.4 ± 2.3	85 ± 13†	7 ± 3	83 ± 14	13 ± 4	78 ± 26
10 min	6.2 ± 2.0	83 ± 13†	7 ± 3	83 ± 14	13 ± 3	75 ± 22
Thiopental						
Base line values	6.9 ± 1.5	95 ± 12	6 ± 4	83 ± 13	13 ± 2	89 ± 29
2 min	6.5 ± 1.6	87 ± 12†	8 ± 5	79 ± 12	13 ± 3	85 ± 27
5 min	6.0 ± 1.3†	87 ± 16	9 ± 5	76 ± 11	13 ± 4	81 ± 23
10 min	6.0 ± 1.3	83 ± 14†	8 ± 4†	78 ± 9	13 ± 3	77 ± 16

* Values are means ± SD. Abbreviations used are: CO, cardiac output; MAP, mean arterial pressure; MRAP, mean right atrial pressure; HR, heart rate; SVR, systemic vascular resistance; SV, stroke volume.

† $p < 0.05$ as compared with base line values.

ences in any measured or derived parameter could be determined for any corresponding point in the study.

DISCUSSION: Expected cardiovascular changes following thiopental administration include a reduction in CO, MAP, and SV, with variable responses in HR and SVR. These effects, including a decrease in HR and an unchanged SVR, were observed in this study. Midazolam is generally ascribed to have minimal hemodynamic effects. Sedative doses of 0.05 mg/kg IV in patients with coronary artery disease produced no cardiovascular changes from control values (1). A similar group of patients receiving midazolam, 0.2 mg/kg IV, after morphine-scopolamine premedication displayed decreased MAP, SV, and SVR; CO was unchanged, perhaps due to a compensatory increase in HR (2). The present study indicates that the only significant cardiovascular changes following induction doses of midazolam in healthy patients are limited to small (16% to 18%) decreases in MAP, whereas CO, HR, SV, MRAP, and SVR tend to be maintained. Although the changes in MAP, CO, and MRAP with thiopental did differ significantly from control values, there were no significant differences between thiopental and midazolam in any of the parameters measured for any corresponding point of measurement. Consequently, from cardiovascular considerations alone, it may be concluded that midazolam is at least as good as thiopental as an anesthesia induction agent in healthy patients.

REFERENCES:
1. Fragen RJ, et al. Anesthesiology 1979;51:S-103.
2. Reves JG, et al. Can Anaesth Soc J 1979;26:402.

Clinical Neuromuscular Pharmacology of BW 33A

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BW 33A (Atracurium) is a new bisquaternary neuromuscular blocking agent being introduced in the United States for initial clinical trials. It is a unique synthetic noncholine diester compound. A summary of our initial clinical experience follows.

METHODS: The study was approved by the institutional Human Subjects Committee. Twenty-five informed and consenting nonobese adult patients, 18 to 48 years of age, A.S.A. class I or II, were studied. All patients passed screening for neuromuscular and cardiovascular abnormalities, and were undergoing narcotic-N_2O-O_2 "balanced" anesthesia for elective surgery following thiopental sodium (4 to 6 mg/kg) induction. Ventilation was controlled at 10 ml/kg, 10 breaths per minute. The first dose of BW 33A was injected after establishment of a steady state of anesthesia. The ulnar nerve was supramaximally stimulated at 0.1 Hz. The compound electromyographic counterpart of the thumb twitch was recorded. Patients were divided into five groups of five patients each. Group I received incremental doses cumulatively until the block reached 90%. Groups II to V received 0.15, 0.21, 0.39, or 0.60 mg/kg, respectively, a single bolus to each patient. Total neuromuscular recovery from the initial block occurred before further use of BW 33A resumed. All data are expressed as means ± SEM; p values were determined after Student's t-tests.

RESULTS: The neuromuscular block of BW 33A was non-depolarizing. The Table presents the potency and recovery rate of the block, as well as the onset and duration of action of a 93% blocking dose. Repeated injection of increments of BW 33A did not increase the potency or duration of block. Once twitches were clearly visible, complete recovery invariably followed soon. The 10% to 95% recovery time averaged 24 ± 1 minutes, observed on 25 occasions in 19 patients. Consequently, reversal was tested in only six patients; all others recovered completely from the last dose of BW 33A without reversal. The reversal was prompt.

At the maximal neuromuscular effect of BW 33A, the systolic pressure averaged 112 ± 3 torr, without statistically significant changes, $p > 0.5$, from pre-BW 33A values of 112 ± 2 torr. The corresponding heart rate was 72 ± 3 beats per minute, with a statistically significant reduction of little clinical significance,

TABLE
Neuromuscular Effects of BW 33A

Group	ED_{50} (mg/kg)	Time to 25%–75% recovery (min)	After 93% blocking dose (min)*	
			Onset	Duration
I	0.21 ± 0.02†	—‡	Not	
	N = 5	11 ± 1	applicable	
II–V	0.20 ± 0.05§	N = 18	4.5 ± 0.9	44 ± 4
	N = 20		N = 6	N = 6

* From those with 84% to 97% block, to represent effect of an ED_{90-95} bolus dose; onset defined as % completion of effect of bolus; duration defined as time taken to recover to 90% of control; both timed from injection of drug to include latency.
† From five cumulative dose-response curves.
‡ From those with initial block greater than 75%.
§ From dose-response curve of 20 points.

from 82 ± 3 beats per minute, $p < 0.01$. No clinical clues of histamine release were observed.

CONCLUSION: BW 33A is a short-acting, nondepolarizing neuromuscular blocking agent with rapid onset, rapid recovery, and minimal cardiovascular effects. Among the ultra-short-acting and the long-acting neuromuscular blockers available for clinical use, BW 33A may have a place in clinical anesthesia.

REFERENCE:
1. Payne JP, Huges R. Evaluation of atracurium in anaesthetized man. Br J Anaesth 1981;53:45–54.

Neuromuscular Blocking Effects of Tobramycin, Gentamicin, and Cefazolin

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Neuromuscular blocking effects of antibiotics and the high mortality rate associated with antibiotic-induced accidental paralysis are well known (1). Eleven of 21 antibiotics with known neuromuscular blocking activity have clinically induced accidental paralysis.

METHODS: This study was performed on 40 male or female patients (A.S.A. class I or II), 18 to 75 years of age with no medical problems and who were undergoing elective surgery. Pregnant women, patients with vestibular or hearing dysfunction, patients with allergies to tobramycin, gentamicin, or cefazolin, patients on diuretics, and patients receiving any antibiotic within 4 days before the study were eliminated from this study. The patients were prospectively and randomly assigned in approximately equal numbers to one of four treatment groups: group A, 1 mg/kg of tobramycin; group B, 1 mg/kg of gentamicin; group C, 500 mg of cefazolin; or group D, control (no antibiotic). All antibiotics were administered intravenously over 45 minutes immediately preceding surgery.

Anesthesia was induced with thiopental, 4 ml/kg IV, and maintained with enflurane 1.0% to 1.5% (inspired) and N_2O-O_2 (2 L:1 L) after endotracheal intubation. The ventilation was approximately 10 ml/kg, 10 breaths per minute controlled with a ventilator. Following induction of anesthesia the prerelaxant neuromuscular response was determined, then succinylcholine (1 ml/kg) was administered, and the effects were monitored. The first dose of *d*-tubocurarine (0.1 ml/kg) was given 5 to 10 minutes after full recovery from succinylcholine.

Single supramaximal stimulus to the ulnar nerve was repeated at 0.1 Hz, interrupted transiently only for other tests. The thumb twitch was recorded and quantified electromyographically.

The neuromuscular response to each dose of *d*-tubocurarine and the time course of block of succinylcholine and *d*-tubocurarine were quantified and compared among groups (*t*-tests). At 75% twitch recovery a train-of-four and a tetanic response were elicited. At the end of the operation, atropine, 0.02 mg/kg, and neostigmine, 0.04 mg/kg, were used to reverse the block.

RESULTS: Base line neuromuscular data, duration of block of succinylcholine, and potency, duration of block, recovery rate, train-of-four fade, tetanic trend, response to double stimuli, post-tetanic effect, and reversibility of the subsequent *d*-tubocurarine-induced neuromuscular block were not found significantly different ($p < 0.01$) when comparison was made between the groups given antibiotics and the control group (Table).

DISCUSSION: Gentamicin and tobramycin are known to possess neuromuscular blocking effects and block neuromuscular transmission in animals at high doses, but they are considered safer than previously popular aminoglycoside antibiotics. Cefazolin is even safer from the viewpoint of neuromuscular blocking side effects. To date, subclinical neuromuscular effects and relaxant potentiating effects of these antibiotics have not been ruled out. Based on the present prospective controlled study, the authors conclude

TABLE

Neuromuscular Data and Other Variables for Four Treatment Groups*

	Group				ANOVA
	Control	Cefazolin	Gentamicin	Tobramycin	*p* value
dTc dose response					
0.1 mg/kg	0.424	0.531	0.293	0.309	0.241
0.2 mg/kg	0.823	0.779	0.841	0.709	>0.5
0.3 mg/kg	0.610	0.840	0.925	0.605	—
ED_{50}	0.125	0.113	0.129	0.157	0.485
T4/T1 at 50% block dTc	0.201	0.217	0.238	0.269	0.270
25%–50% recovery time	20.50	17.25	21.80	18.05	>0.5
Time for 50% gain reversal	2.67	2.60	2.75	3.24	>0.5
R2/R1 (T1) at 50% block	—	0.447	0.447	—	>0.5

* Abbreviation used is: dTc, *d*-tubocurarine.

that tobramycin, gentamicin, and cefazolin, in recommended single doses, lack clinical and subclinical relaxant-potentiating neuromuscular effects and do not differ from one another in this respect.

REFERENCE:
1. Pittinger C, Eryasa Y, Adamson R. Antibiotic-induced paralysis. Anesth Analg 1970;49:487–501.

Hemodynamics during Anesthesia in the Seated Position

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A well recognized problem associated with anesthesia in the seated position is cardiovascular instability. We, therefore, undertook an investigation of the hemodynamic effects of four different anesthetic techniques in patients placed in the seated position.

METHODS: The subjects of this study were 24 consecutive patients (A.S.A. class I or II), aged 22 to 64 years, scheduled for neurosurgical operations. They were assigned randomly to four groups of six each according to the anesthetic technique used. The patients were premedicated with morphine, 0.1 mg/kg, and atropine, 0.4 mg, intramuscularly, and diazepam, 0.1 mg/kg, orally 1 hour before beginning the study period. Upon arrival in the operating suite, radial arterial and thermistor-tipped pulmonary arterial catheters were placed, and the patient's legs were wrapped with elastic bandages. Base line hemodynamic data were obtained with the patient awake and in the supine position.

Anesthesia was induced with thiopental sodium, 3 mg/kg IV, and endotracheal intubation was facilitated with pancuronium, 0.1 mg/kg IV. Anesthesia was maintained with 60% N_2O in O_2 and supplemented with one of four agents: (*a*) morphine sulfate, 0.5 mg/kg IV; (*b*) Innovar, 0.1 ml/kg IV; (*c*) halothane 0.4% end-tidal, or (*d*) enflurane 0.7% end-tidal. Hemodynamic data were collected after 10 minutes of stable anesthesia with the patient supine and again 5 minutes after the patient was placed in the seated position. This protocol was approved by the institution's Human Studies Committee, and informed consent was obtained from all subjects.

RESULTS: During anesthesia, placement in the seated position resulted in significant decreases in mean systemic arterial pressure in the groups given Innovar [−24 ± 8 (SE) torr], halothane (−21 ± 6 torr), and enflurane (−23 ± 6 torr) as compared with awake supine control values (Table). In the group given morphine anesthesia there was no significant change in systemic arterial pressure as compared with awake supine control values.

TABLE

Comparative Hemodynamic Data*

	Awake supine control	Anesthesia-seated	Change from control
Morphine			
SAP	85 ± 4	79 ± 4	−7 ± 5
CI	4.28 ± 0.14	3.20 ± 0.37†	−1.08 ± 0.39
SVI	57 ± 4	39 ± 2†	−17 ± 4
SVR	770 ± 40	996 ± 119	+226 ± 101
PRA	1.55 ± 0.71	1.20 ± 0.46	−0.348 ± 0.75
Innovar			
SAP	93 ± 4	69 ± 5†	−24 ± 8
CI	3.32 ± 0.14	2.60 ± 0.22†	−0.72 ± 0.18
SVI	51 ± 2	36 ± 4†	−14 ± 2
SVR	1109 ± 90	1083 ± 34	−26 ± 73
PRA	2.70 ± 1.35	1.96 ± 0.40	−0.74 ± 1.39
Halothane			
SAP	102 ± 5	80 ± 2†	−21 ± 6
CI	3.68 ± 0.27	2.45 ± 0.17†	−1.23 ± 0.19
SVI	53 ± 1	29 ± 3†	−23 ± 3
SVR	1165 ± 116	1375 ± 100	+211 ± 138
PRA	1.34 ± 0.78	2.30 ± 0.62	+0.953 ± 0.713
Enflurane			
SAP	87 ± 3	64 ± 3†	−23 ± 6
CI	3.67 ± 0.38	2.50 ± 0.28†	−1.17 ± 0.24
SVI	53 ± 5	32 ± 4†	−21 ± 5
SVR	993 ± 102	1107 ± 201	+114 ± 154
PRA	1.33 ± 0.62	4.51 ± 2.82	+3.18 ± 2.43

* Values are means ± SE. Abbreviations used are: SAP, systemic arterial pressure (torr); CI, cardiac index (L/min/m^2); SVI, stroke volume index (ml/beat/m^2); SVR, systemic vascular resistance (dyne/sec/cm^5); PRA, plasma renin activity (mg/ml/hr).

† Significant difference from control value.

The group given morphine exhibited relatively minor decreases in cardiac index (−25% ± 9%) and stroke volume index (−30% ± 5%). The volatile agents resulted in larger decreases in cardiac index (−32%) and stroke volume index (−42%); indicating that the decrease in systemic arterial pressure in the groups given halothane and enflurane was the result of myocardial depression. The decrease in systemic arterial pressure in the group given Innovar was primarily due to a less stable systemic vascular resistance than was seen with the other anesthetic techniques.

Plasmin renin activity did not change in the seated position under anesthesia in any of the groups as compared with awake supine control values (Table).

CONCLUSION. Our data thus indicate that: (*a*) for operations in the seated position, morphine-N_2O-O_2-relaxant anesthesia results in the greatest cardiovascular stability among the techniques studied, and (*b*) inhibition of the normal release of renin may contribute to cardiovascular instability in the seated possition.

Pancuronium and Metocurine or *d*-Tubocurarine Do Not Compete for the Same Binding Sites in Plasma or Tissues

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The neuromuscular blocking effect of pancuronium (Pm)-metocurine (mTc) and Pm- *d*-tubocurarine (dTc) combinations were significantly more potent than additive effects of each of the individual drugs given alone (1). Such potentiation of drug effects has been shown when two drugs having common nonspecific binding sites are used in combination (e.g., coumadin and oral hypoglycemics). We have investigated the possibility that competition between Pm and dTc or mTc for the same nonspecific binding sites in plasma or tissue may result in greater than normal free concentration of both drugs and may be responsible for the potentiating effect at the neuromuscular junction when used in combination.

MATERIALS AND METHODS: In the in vitro study, using plasma from six healthy volunteers, equilibrium dialysis was accomplished as described previously (2) using ^{3}H-dTc and cold Pm at various concentrations (Table 1), and the subsequent binding of dTc in the absence or presence of Pm was evaluated. Thus, a matrix of six experiments at three concentrations was run for each donor plasma to determine whether increasing concentrations of Pm will result in lower dTc binding. In the in vivo study, five burned patients who were recovering from neuromuscular paralysis from mTc, were given Pm, 1 mg, intravenously to determine whether the administration of Pm resulted in displacement of mTc from nonspecific binding sites. Thus, the twitch height and the plasma mTc concentration before and after Pm were measured (Table 2).

RESULTS: With increasing Pm concentrations the binding of dTc did not significantly change in vitro (Table 1, $p > 0.05$); similarly, the mTc concentration in plasma did not increase subsequent to the intravenous administration of Pm.

TABLE 1
Drug Concentration Percent Bound*

	dTc alone	dTc + Pm
Low dTc (0.007 μg/ml) High Pavulon (1.1 μg/ml)	28.9 ± 3.7	27.5 ± 3.1
Medium dTc (0.78 μg/ml) Medium Pavulon (0.22 μg/ml)	30.7 ± 4.1	29.0 ± 4.4
High dTc (39 μg/ml) Low Pavulon (0.022 μg/ml)	27.1 ± 3.1	23.8 ± 3.2

* Values are means ± SD.

TABLE 2
Twitch Height and Plasma mTc Concentration

mTc concentration		Twitch height (% control)	
Pre-Pm	Post-burn	Pre-Pm	Post-Pm
μg/ml			
0.31	0.30	83	0
1.69	1.56	73	0
0.41	0.37	73	0
0.41	0.38	69	14
0.46	0.45	72	8

DISCUSSION: Potentiating effect of the dTc-Pm or mTc-Pm combinations can be explained by a nonspecific competitive binding model only if these drugs bind to identical sites or if conformational changes induced by the binding of one drug affect the binding of the other. The selection of high and low dosage pairs (Table 1) allowed sufficient testing of this model with only one radio-labeled drug. If the model is correct, as Pm concentration is increased, dTc plasma binding should decrease. Similarly, in vivo, if there is displacement of mTc from tissue binding sites by Pm, the plasma concentration should increase following the administration of Pm due to displacement of mTc by Pm from nonspecific binding sites. The data suggest strongly that Pm has little effect on the binding of dTc or mTc to plasma and tissues. Thus, competitive binding cannot explain the potentiating effect of these two combinations.

REFERENCES:
1. Lebowitz PW, Ramsey FW, Savarese JJ, et al. Potentiation of neuromuscular blockade in man produced by combinations of pancuronium and metocurine or pancuronium and *d*-tubocurarine. Anesth Analg 1980;59:604–9.
2. Leibel WS, Martyn JAJ, Szyfelbein SK, et al. Anesthesiology 1981;54:378–82.

Isoniazid Induces Enflurane Defluorination in Man

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Peak serum inorganic fluoride (F^-) levels following enflurane anesthesia, with rare exceptions, have been less than 50 μM. This study was prompted by a case in which a level of 106 μM occurred in a patient treated with isoniazid (INH; isonicotinic acid hydrazide), associated with a mild urinary concentrating defect.

METHODS: Twenty surgical patients treated with INH then anesthetized with enflurane were studied. Duration of INH treatment varied from 1 week to 11 months; all patients received 300 mg daily. The conrol group consisted of 36 patients anesthetized with enflurane who were receiving no drugs. Serum F^- was measured before and 1, 3 to 6, 24, and 48 hours after anesthesia. Blood urea nitrogen and creatinine levels were measured before and after surgery.

RESULTS: Individual peak serum F^- levels and the linear regression of peak serum F^- on hours of enflurane administration were compared for both groups of patients. Nine of the 20 INH-treated subjects appeared to represent a different population than the other 11 INH-treated patients and the 36 control patients. Peak F^- values for the nine patients exceeded levels predicted by regression analysis by 200% to 400%; in three patients peak values exceeded 100 μM. No other peak F^- level exceeded predicted values by more than 50%. There were no changes in postoperative blood urea nitrogen and creatinine levels.

DISCUSSION. The present study defines two distinct responses to INH treatment: one characterized by increased enflurane defluorination; the other, by normal defluorination. In other studies, treatment with INH and its hydrazine (NH_2-NH_2)-containing metabolites enhanced in vitro hepatic microsomal enflurane defluorination by 3- to 4-fold, and in vivo defluorination in Fischer 344 rats by 4-fold. However, treatment of surgical patients or experimental animals with enzyme-inducing agents that do not contain the hydrazine moiety, did not increase enflurane defluorination. INH metabolism is polymorphic in humans. Rapid acetylation occurs in approximately 50% of Americans with enhanced formation of acetylisonicotinic acid hydrazide and, subsequently, of hydrazine. We speculate that rapid acetylators of INH have higher F^- values than slow acetylators because high hydrazine levels induce enflurane defluorination.

Release of Catecholamines by Succinylcholine in Man

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The hypothesis that some adverse reactions to succinylcholine (SCh) may be due to its nicotinic effect has been tested. If true, then SCh-induced catecholamine release may precipitate the frequently observed hypertension and tachyarrhythmias with SCh.

MATERIALS AND METHODS: Seven premedicated adults (promethazine, 25 mg IM; scopolamine, 0.3 mg IM) were monitored by electrocardiogram and blood pressure cuff. Following intravenous and radial artery cannulation, anesthesia was induced with thiopental (4 mg/kg IV) and maintained with N_2O-O_2 (50-50) and halothane (1% to 1.5%). Ventilation was assisted by mask. After stabilization of ventilation and hemodynamics, SCh (1 mg/kg) was administered as an intravenous bolus. Orotracheal intubation was performed after disappearance of fasciculations.

Arterial blood samples were collected: (*a*) immediately before thiopental injection, (*b*) immediately before SCh injection, (*c*) 2 minutes after SCh injection but before intubation, (*d*) 1 minute after intubation, and (*e*) 10 minutes after SCh injection.

Samples were analyzed for sodium, potassium (ion specific electrodes), calcium, blood gases, norepinephrine, and epinephrine (Peuler and Johnson radioenzymatic technique).

RESULTS: In five of the seven patients, results were similar. SCh, before endotracheal intubation, produced a significant increase in blood pressure and heart rate ($p < 0.05$). Mean increase in plasma potassium was 0.360 meq/L. Plasma epinephrine did not increase significantly. Mean plasma norepinephrine increased from 301.4 to 490.6 pg/ml ($p < 0.005$). Of the remaining two patients, one had an 8-fold increase in plasma norepinephrine, and the other had a 10-fold increase accompanied by bigeminy.

CONCLUSIONS: Administration of SCh causes an abrupt elevation of plasma norepinephrine. The increase may reach 1000% of normal and 7 times the measured exercise level (1). We conclude that this norepinephrine release contributes to the hypertension and tachyarrythmias observed following SCh administration.

REFERENCE:
1. Johnson G, Peuler J, Baker C. Plasma catecholamines in normotensive subjects. Curr Ther Res 1977;21:898-908.

Duration of Pancuronium Neuromuscular Blockade in Patients Taking Anticonvulsant Medication

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The observation that the duration of pancuronium-induced neuromuscular blockade is shorter in patients taking anticonvulsant medications before surgery than in comparable patients not on such medications prompted this prospective study.

Nineteen adult neurosurgery patients with no known neuromuscular pathology were studied. Eleven patients were receiving anticonvulsant therapy before surgery, whereas eight control patients were not. The two groups were comparable as to patient age and A.S.A. physical status. Preoperative electrolyte levels and available blood levels of anticonvulsant drugs were recorded. In all patients anesthesia was induced with thiopental and maintained with a N_2O-O_2-narcotic-relaxant technique using fentanyl. Pancuronium bromide, 0.1 mg/kg, was administered intravenously to facilitate endotracheal intubation. Intubation was accomplished when all four twitches in a train-of-four pattern produced by percutaneous ulnar or median nerve stimulation with a Bard Biomedical Peripheral Nerve Stimulator (model 750 digital) were abolished. The train-of-four pattern was monitored throughout anesthesia at a minimum of 10-minute intervals and pancuronium administered as needed to maintain loss of the third and fourth twitches.

The time interval (mean ± SEM) between the initial dose and the second dose of pancuronium was 45 ± 5 minutes in the patients on anticonvulsant therapy and 102 ± 6 minutes in the control patients.

Cardiovascular and Pulmonary Effects of Serotonin Antagonism before and during Endotoxic Shock in Dogs

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Many of the cardiovascular and pulmonary effects of endotoxic shock are related to the liberation of serotonin. This study was designed to evaluate the cardiovascular and pulmonary effects of ketanserin, a specific serotonin receptor blocker, in dogs before and during endotoxic shock.

METHODS: Twelve mongrel dogs were anesthetized with thiopental, intubated, and mechanically ventilated to maintain $Paco_2$ at 33 to 38 torr. Following implantation of arterial, intravenous, and thermodilution pulmonary artery catheters, the animals received a loading bolus of 30 ml/kg of Ringer's lactate followed by maintenance dosage of 8 ml/kg/hr. The dogs were divided into three groups. Group I consisted of four dogs infused with *Escherichia coli* endotoxin (Difco Laboratories), 2 mg/kg, and served as the control group. The remaining eight dogs were treated with ketanserin (5-mg bolus, then 2 mg/hr); four dogs (group II) received ketanserin 5 minutes before the endotoxin injection and four (group III) received ketanserin 5 minutes after the endotoxin injection.

RESULTS: Ketanserin alone produced no change in any cardiovascular variable measured. All groups sustained significant decreases in mean arterial pressure, mean pulmonary artery pressure, and cardiac output, as well as significant increases in systemic vascular and pulmonary vascular resistance following endotoxin administration. Both groups treated with ketanserin sustained significantly less decline in mean arterial pressure, mean pulmonary artery pressure, and cardiac output as well as significantly less increase in systemic vascular and pulmonary vascular resistance compared with the control group. Blood sugar, base deficit, pulmonary shunt fraction, and oxygen were not significantly different between the ketanserin-treated group and the control group at any time during the study. Ketanserin also significantly increased survival time whether administered before or after endotoxin.

DISCUSSION AND CONCLUSIONS: The data indicate that the cardiovascular alterations produced by endotoxic shock can be antagonized following treatment with ketanserin and minimized by pretreatment with the drug. Ketanserin also appears to increase survival time in dogs with endotoxic shock.

Rate-Pressure Product Correlates Poorly with MV_{O_2} during Anesthesia in Coronary Patients

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The accuracy and usefulness of indirect indicators of myocardial oxygen consumption (MV_{O_2}) are of great current interest. The important question is: do simple measurements, such as rate-pressure product (RPP) and triple-product (TP) accurately monitor MV_{O_2} in coronary disease? As major determinants of MV_{O_2}, systolic pressure (reflecting tension) is multiplied by rate to give RPP. Systolic ejection time, another important factor in MV_{O_2}, is multiplied by RPP to give TP.

In 13 awake coronary patients Baller et al (1) found close correlations of RPP and TP with MV_{O_2} ($r = 0.91$ and 0.94). In 16 coronary patients, having morphine or halothane and nitrous oxide, Wilkinson et al (2) found a significant relationship between RPP and MV_{O_2}.

We examined the correlation of MV_{O_2} to RPP and TP in 26 patients having coronary vein grafts. A radial needle and two thermodilution catheters were placed

TABLE

Correlation Coefficients and *p* Values for Rate-Pressure Product (RPP) in the Groups

RPP	Total group (n = 26)	Less Outliers
Awake		
r	0.45	0.09
p	<0.06	NS*
Postinduction		
r	0.52	0.04
p	<0.05	NS*
Postintubation		
r	0.62	0.32
p	<0.05	NS†
Presternotomy		
r	0.75	0.73
p	<0.05	<0.05*
Poststernotomy		
r	0.55	0.38
p	<0.05	NS*

* n = 25.
† n = 23.

(*a*) into the pulmonary artery and (*b*) into the coronary sinus by fluoroscopy. Total coronary sinus blood flow, multiplied by the arterial to coronary sinus O_2 content difference = MV_{O_2} (ml/min).

Repeated measures regression analyses were done separately from data collected: (*a*) awake, (*b*) postinduction, (*c*) postintubation, (*d*) presternotomy, and (*e*) poststernotomy, as the inclusion of all the data points for each subject in one regression analysis likely violates the assumption of independent error terms. Also the regression models were done (*a*) with and (*b*) excluding outliers (data points distant from the rest). The Table shows correlation coefficients and *p* values for the latter two groups. Using all data points, there were significant correlations of MV_{O_2} to RPP in all series, as was found by Wilkinson (2). However, when the outlying points were excluded, significant relations were present only presternotomy. Similar results occurred with MV_{O_2} and TP. That is, no correlation was found when awake or at four of five study series during anesthesia.

We found in 26 patients that (*a*) the statistical methods influence the results and (*b*) during morphine or halothane anesthesia in coronary patients, no significant, useful, or precise relationship exists between RPP or TP and MV_{O_2}.

REFERENCES:

1. Baller D. et al. Comparison of myocardial oxygen consumption indices in man. Clin Cardiol 1980;3:116–22.
2. Wilkinson PL, et al. Rate-pressure product and myocardial oxygen consumption during surgery for coronary artery bypass. Circulation 1979;60:Supp 1:170–3.

Is Right Atrial Catheterization Always Indicated for Anesthesia in the Sitting Position?

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Previously we used right atrial catheterization (RAC) in more than 200 patients who underwent posterior fossa craniectomy and nerve decompression in the sitting position for hemifacial spasm or trigeminal neuralgia. There were no apparent benefits from RAC in this group of patients; however, there were several serious complications including three pneumothoraces. It was therefore decided to omit RAC in subsequent operations of this category.

METHOD: Thirty-four patients underwent posterior fossa craniectomy for nerve decompression in the sitting position. Anesthesia consisted of diazepam, thiopental, pancuronium, succinylcholine, meperidine, nitrous oxide, and oxygen. Pa_{O_2} was maintained at approximately 30 torr using controlled mechanical ventilation. A Versatone Doppler precordial probe was carefully positioned and tested by injecting 1 ml of air intravenously at the outset. During the operations, when the Doppler indicated the apparent entry of air the surgeon was notified, nitrous oxide administration was discontinued, and either positive end-expiratory pressure (PEEP) hyperinflation of lungs, jugular venous compression, or a combination of these maneuvers was used.

RESULTS: Changes in the Doppler sound suggesting air embolism occurred in 12 cases (35%). The average duration of the abnormal sound was approximately 5 minutes (ranging from 1 to 13 minutes) and during these times there were no significant changes in vital signs. PEEP, hyperinflation maneuver, and/or jugular venous compression was used in 11, nine, and three cases, respectively. All patients recovered from the operative procedure and there were no neurologic deficits attributable to air embolism.

CONCLUSION: The incidence of air embolism in posterior fossa craniectomies for nerve decompression is high, but the amount of air entrained is clinically insignificant if detected early and appropriate measures are carried out promptly. Attempts to aspirate moderate amounts of air in this situation might only divert the attention of the anesthesiologist from the more important task—that of preventing the further entry of significant quantities of air. In the particular circumstances described, we believe that RAC is not justified, because it has no advantage and subjects the patients to unnecessary risks.

Continuous Infusion of Fentanyl for Cardiac Surgery

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Anesthetic doses of fentanyl (F) are usually determined empirically; 50 to 150 μg/kg have been used, with most of the dose given before cardiopulmonary bypass (CPB) when stimulation is intense. Following F doses of 75 μg/kg for induction of anesthesia, many of our patients became hypertensive and responsive to commands after CPB, when their plasma F levels were less than 10 ng/ml (unpublished data). We designed a F infusion technique to: (*a*) provide plasma F concentrations before CPB comparable to those produced by a "bolus" injection, and (*b*) to maintain concentrations at ≥20 ng/ml after CPB.

METHODS: Six patients undergoing myocardial revascularization received propranolol (10 to 40 mg), Nitrol ointment (1 inch), morphine (0.1 mg/kg IM), and lorazepam (2 mg orally) 2 hours before surgery. After preanesthetic preparations, both the loading (2.4 μg/kg/min for 20 minutes) and continuous F infusions (0.3 μg/kg/min until the end of surgery) were begun at rates calculated to provide a peak F concentration of 80 ng/ml and a stable F concentration of 20 ng/ml of plasma (1). Arterial plasma was analyzed for F by radioimmunoassay. Patients were ventilated with 100% oxygen and received either *d*-tubocurarine or pancuronium. Ulnar nerve stimulation was used to monitor relaxation, while avoiding complete paralysis.

RESULTS AND DISCUSSION: Patients received a total F dose of 106 ± 2.4 μg/kg (mean ± SE). The loading infusion produced F concentrations approximating those following a bolus injection before CPB, and the continuous infusion maintained concentrations at 20 ± 1 ng/ml thereafter (Figure). These levels were adequate to maintain heart rate and blood pressure within ±20% of preanesthetic values. Slight responsiveness of one patient to stimulation after CPB was abolished with 50 mg of thiopental. All patients became responsive at F levels averaging 8.6 ± 1.1 ng/ml and could be extubated 19 ± 1 hours after surgery when F levels were 2.9 ± 0.1 ng/ml. We conclude that constant, predictable plasma F levels can be produced under clinical conditions. They provide a stable anesthetic level and facilitate the study of dose-response relationships.

REFERENCE:
1. Wagner JD. A safe method for rapidly achieving plasma concentration plateaus. Clin Pharmacol Ther 1974;16:691–700.

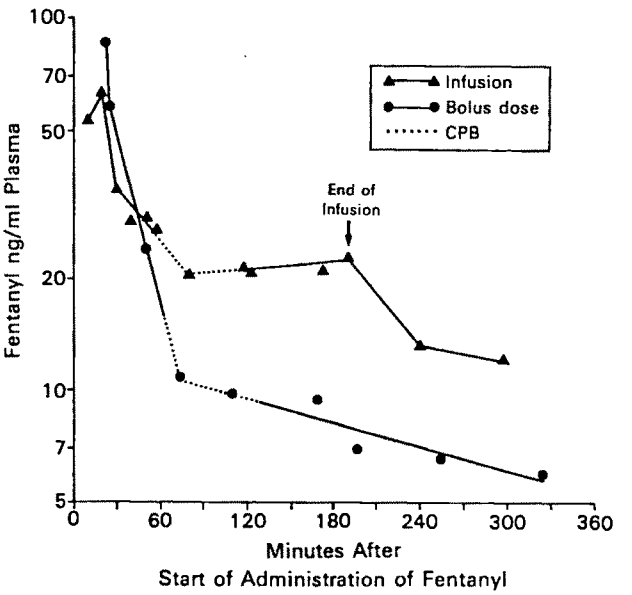


FIGURE. Fentanyl concentrations in plasma of patients during cardiac surgery. Bolus dose (75 μg/kg) was administered over 20 minutes (unpublished data). Loading and continuous infusions are described under "Methods." Duration of cardiopulmonary bypass (CPB) is indicated by dotted lines. Each data point is mean value for six patients; standard error is less than ±10% for each point.

Isoflurane versus Enflurane in Aortic Stenosis

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Potential benefits of isoflurane (I) in volunteers without heart disease include maintenance of cardiac output, with increased heart rate compensating for decrease stroke volume (1). Patients with coronary artery disease receiving I have been shown to have nonstatistically significantly decreased cardiac index and a 20% decrease in mean arterial pressure (2). Enflurane (E) is a known myocardial depressant. This study was designed to determine whether any difference existed between the hemodynamic effects of I and E on patients with aortic stenosis.

METHODS: Ten patients with aortic stenosis (>50 mm Hg gradient) and without coronary artery disease undergoing valve replacement were studied. Both agents were available for clinical use and Human Studies Committee approval was not required. Equi-MAC concentrations of I (0.45 MAC, 0.5%) in five patients (group 1) and E (0.44 MAC, 0.75%) in five patients (group 2) were used with 30% O_2/70% N_2O after induction with fentanyl, 25 μg/kg, and relaxation with pancuronium, 0.1 mg/kg. Hemodynamic profiles (cardiac index, mean arterial pressure, heart rate,

TABLE

Hemodynamic Parameters before Intubation (A), at Skin Incision (B), at Sternotomy (C), and Immediately before Bypass (D)*

	A	B	C	D
CI (L/min/m^2)				
I	2.7 ± 0.2	2.5 ± 0.2	2.4 ± 0.2	2.3 ± 0.1†
E	2.9 ± 0.2	2.4 ± 0.1†	2.3 ± 0.1†	2.3 ± 0.2†
MAP (mm Hg)				
I	86 ± 2.1	75 ± 2.4†	64 ± 3.2†	71 ± 3.4†
E	83 ± 3.0	76 ± 2.8	70 ± 2.4†	65 ± 2.8†
HR (beats/min)				
I	88 ± 2.0	86 ± 2.2	86 ± 2.3‡	82 ± 1.9†
E	84 ± 1.6	80 ± 2.0	78 ± 1.8†	76 ± 1.9†
SVI (ml/beat/m^2)				
I	30.7 ± 3.1	28.5 ± 2.8	27.3 ± 3.2	27.8 ± 2.9
E	34.5 ± 4.0	30.0 ± 3.4	29.4 ± 2.8	29.6 ± 3.0
SVR (dynes·sec·cm^{-5})				
I	1,339 ± 54	1,238 ± 47	1,060 ± 43‡	1,271 ± 73
E	1,216 ± 48	1,340 ± 62	1,263 ± 54	1,232 ± 50
PVR (dynes·sec·cm^{-5})				
I	104 ± 13	133 ± 21	100 ± 12	123 ± 16
E	100 ± 16	100 ± 13	105 ± 17	129 ± 15
RPP				
I	10,035 ± 806	9,030 ± 698	8,600 ± 573	7,790 ± 659†
E	9,324 ± 714	8,480 ± 542	7,800 ± 469	7,144 ± 638†

* Values are means ± SEM. Abbreviations used are: I, isoflurane; E, enflurane; CI, cardiac index; MAP, mean arterial pressure; HR, heart rate; SVI, stroke volume index; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; RPP, rate-pressure product.

† $p < 0.05$ vs E by Student's *t*-test for paired values.

† $p < 0.05$ vs A by Student's *t*-test for unpaired values.

stroke volume index, systemic vascular resistance, pulmonary vascular resistance, and rate-pressure product) were obtained before intubation (A), at skin incision (B), at sternotomy (C), and before bypass (D).

RESULTS: Data are shown in the Table. Cardiac index was equivalently depressed with both agents at time D. Mean arterial pressure decreased equivalently with both I (17%) and E (22%). Heart rate and rate-pressure product were generally nonsignificantly higher with I than E, although decreases in rate-pressure product were seen with both agents. Stroke volume index remained unchanged. Decreased systemic vascular resistance was seen only with I at time C.

DISCUSSION: Maintenance of cardiac output with I under these conditions was not seen. An expected higher heart rate with I was seen, although global myocardial oxygen consumption ($M\dot{V}_{O_2}$), as gauged by rate-pressure product, decreased. Patients with aortic stenosis may respond differently to I than non-diseased patients or patients with coronary artery disease. The data do not support a hemodynamic superiority of I over E in patients with aortic stenosis.

REFERENCES:

1. Stevens WC, Croswell TH, Halsey MJ, et al. The cardiovascular effects of a new inhalation anesthetic, Forane, in human volunteers at constant arterial carbon dioxide tension. Anesthesiology 1971;35:8-16.
2. Mallow JE, White RD, Cucchiara RF, et al. Hemodynamic effects of isoflurane and halothane in patients with coronary artery disease. Anesth Analg 1976;55:135-8.

Differential Lung Ventilation following Unilateral Hydrochloric Acid Aspiration in the Dog

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Recent reports claim improved pulmonary gas exchange using differential lung ventilation to treat severe unilateral lung injury. We believe that this disease would be better treated if each lung were ventilated in proportion to its CO_2 excretion. We systematically compared three modes of ventilation following unilateral lung injury in the dog.

METHODS: Eighteen dogs were anesthetized with pentobarbital (30 mg/kg), intubated with a double-lumen endobronchial tube, and mechanically ventilated ($F_{I_{O_2}} = 0.21$) with two microcomputer-controlled Siemens Servoventilators at a total tidal volume of 15 ml/kg and a respiratory rate sufficient to keep the arterial P_{CO_2} at 35 ± 2 torr. A unilateral injury was

induced by the injection of hydrochloric acid (HCl), 2.5 ml/kg, into one lumen of the endobronchial tube. Measurements were made before the acid injection and every 30 minutes for the following 4 hours.

Six dogs were ventilated with equal pause pressure to each lung. Six animals were ventilated with equal volumes (7.5 ml/kg) to each lung. Six animals were ventilated with the tidal volume to each lung which maintained equal end-tidal CO_2 concentrations from both lungs.

RESULTS: There was a significant difference between injured and noninjured lung gas exchange and mechanics following the HCl injury. Postmortem examination showed a 100% increase in the injured lung weight over the uninjured lung weight.

Changes in Pa_{O_2} for the three treatment groups following the HCl injury are shown in the Figure. The group with equal end-tidal P_{CO_2} produced a significantly higher Pa_{O_2} before the injury. The Pa_{O_2} remained higher throughout the course of the HCl injury. The shunt fraction started lower and remained lower in those animals ventilated with the equal end-tidal CO_2 control algorithm.

CONCLUSION: Three modes of differential ventilation have been evaluated following an acute pulmonary injury. Our data suggest that end-tidal CO_2 monitoring and control is the preferred method of controlling short-term differential lung ventilation following acute pulmonary injury.

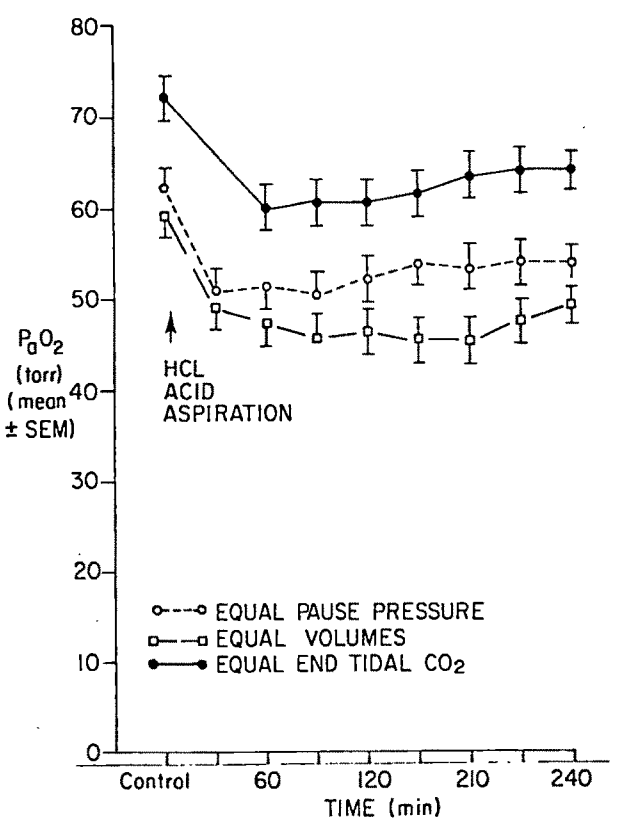


FIGURE. Changes in Pa_{O_2} for three treatment groups following HCl injury.

This work was supported by a grant from the National Heart, Lung and Blood Institute (HL25553-01), Siemens-Elema, and Biochem Int.

Direction of the Needle Bevel and Epidural Anesthetic Spread

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Many factors can influence the spread of local anesthetic solution in the epidural space. A review of the literature, however, failed to reveal any data documenting the effect of the direction of the bevel of the epidural needle on epidural anesthetic spread. This study was designed to evaluate what influence, if any, the direction of the epidural needle bevel during anesthetic injection had on the spread of epidural anesthetic.

METHOD: After obtaining informed consent for the proposed surgery and anesthesia, epidural block was performed on 150 male adults with a mean age of 49 years and a mean height of 177 cm, using a fixed volume of 15 ml of 1.5% lidocaine with epinephrine (1:200,000). Seventy-five patients received an epidural injection of local anesthetic with the bevel of the epidural needle pointing cephalad (cephalad group) and another 75 patients with the bevel of the needle pointing caudad (caudad group). The patient was placed in the lateral position on a horizontal operating room table. A #17 Tuohy needle was introduced into the third lumbar intervertebral space and the epidural space was identified by "loss of resistance" technique. With the level of the needle pointing either cephalad or caudad, anesthetic solution was injected at the rate of 0.7 ml/sec. The spread of sensory anesthesia was then checked every 10 minutes by pinprick and the arithmetic mean of the analgesic spread on each side determined. Student's *t*-test was used for the statistical analysis of the paired data.

RESULTS: Data are summarized in the Table. Mean heights of the patients in both cephalad and caudad groups were similar in comparable age groups. All patients investigated had caudad spread of anesthesia to the end of the sacrum. In 20- to 39-year-old patients there were no significant differences in cephalad spread of epidural anesthesia between cephalad and

TABLE

Relationship between Direction of Bevel of Epidural Needle and Anesthetic Spread in Epidural Space

Group	Upper level of anesthesia* (thoracic dermatome) with bevel direction:		p
	Cephalad	Caudad	
20–39 yr	8.6 ± 0.4	9.2 ± 0.5	0.19
40–59 yr	5.2 ± 0.4	6.2 ± 0.4	<0.05
60–79 yr	4.4 ± 0.5	5.9 ± 0.4	<0.02

* Values are means ± SEM. In each age group, there were 50 patients (cephalad group, 25; caudad group, 25).

caudad groups. However, in patients older than 40 years of age the cephalad spread of epidural anesthesia was significantly higher in the cephalad group than in the caudad group. In both cephalad and caudad groups the upper levels of anesthesia were significantly higher in patients older than 40 years of age than they were in younger patients.

CONCLUSION: When 15 ml of 1.5% lidocaine with epinephrine (1:200,000) was injected into the epidural space, the direction of the bevel of the epidural needle during injection produced a significant effect on the epidural spread of local anesthetic only in patients older than 40 years of age. It is known that as a patient ages, the tissues around the epidural space, i.e., dura and ligamentum flavum, become fibrotic and calcified. When the direction of the needle bevel is changed, this resultant decrease in complicance in older patients could have caused the uneven epidural anesthetic spread.

Diazepam Sedation Reduces Functional Residual Capacity and Alters the Distribution of Ventilation in Man

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Although there is considerable information about the pulmonary dysfunction associated with anesthetizing doses of central nervous system depressants (1), little is known of possible effects of smaller doses, such as remain in patients during recovery from anesthesia. The purpose of this study was to assess global lung volumes and the distributions of lung volume, ventilation ($\dot{V}$), and perfusion ($\dot{Q}$) during sedation produced with intravenous diazepam.

METHODS: Five healthy volunteers (aged 21 to 38) were studied in the right lateral decubitus position while awake and then during sedation. Diazepam, 0.04 mg/kg, was administered intravenously every 3 to 5 minutes as required to induce and maintain a state of sedation that was moderately heavy but did not compromise cooperation needed for the tests. Variables measured in each state were (*a*) minute ventilation, (*b*) static lung volumes (helium dilution and spirometry in duplicate), and (c) regional functional residual capacity/total lung capacity (FRC/TLC) ratios, $\dot{V}$, and $\dot{Q}$ (^{127}Xe inhalation and intravenous bolus injection). Global volumes and regional variables were measured on separate occasions but with diazepam administration on each occasion the same.

RESULTS: Periods of sedation ranged from 32 to 54 minutes. Total doses of diazepam required were 0.16 to 0.38 mg/kg. Sedation did not alter minute ventilation, but reduced tidal volume (0.59 ± 0.05 to 0.42 to 0.05 L, means ± SEM, $p < 0.01$) and increased breathing frequency (15 ± 1 to 21 ± 2 breaths/min, $p < 0.01$). Sedation reduced FRC (2.93 ± 0.25 to 2.78 ± 0.26 L, $p < 0.01$), but TLC and residual volume were unchanged. Sedation also diminished the gradient of ventilation from nondependent to dependent lung (Figure, $p < 0.01$) and, in two subjects, resulted in virtual cessation of dependent zone ventilation during spontaneous episodes of small tidal volumes (approximately 200 ml). There were no detectable changes in regional FRC/TLC ratios or perfusion.

We conclude that moderately heavy diazepam sedation reduces both global FRC and the normal gradient of ventilation by magnitudes somewhat less than those previously observed with intravenous and inhalational anesthesia (1). Disturbances in regional ventilation appear greater when spontaneous tidal volumes are very small. These effects of the sedated state may contribute to the impairment of intrapulmonary gas exchange often present during recovery from anesthesia.

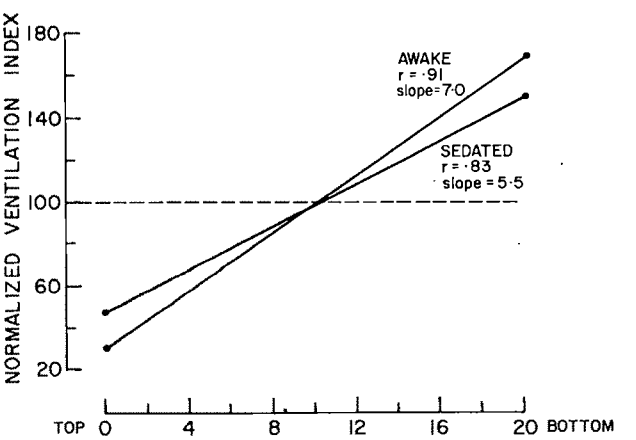


Figure. Distribution of ventilation.

REFERENCE:
1. Rehder K, Sessler AD, Marsh HM. General anesthesia and the lung. Am Rev Respir Dis 1975;112:541-62.

Relationship between Maternal Pa_{O_2} and Fetal Oxygenation during Cesarean Section under Epidural Anesthesia

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Hyperoxia causes placental vasoconstriction in direct perfusion experiments. Rorke et al (1) reported that fetal oxygenation decreased with maternal Pa_{O_2} greater than 300 torr during cesarean sections under general anesthesia. This was not confirmed by Marx and Mateo. Our study assesses fetal oxygenation with increasing maternal Pa_{O_2} during cesarean sections under epidural anesthesia.

METHODS: Forty healthy consenting patients scheduled for elective cesarean sections were studied. Following hydration (1500 ml of Hartman's solution) epidural anesthesia was induced to T-4 level using 18 to 22 ml of 0.75% bupivacaine. Left uterine displacement was maintained. Patients (n = 10 per group) breathed a F_{IO_2} of 0.21 (group A), 0.47 (group B), 0.74 (group C), and 1.0 (group D). The oxygen (in N_2 in groups A, B, and C) was inhaled from a tight-fitting mask and delivered through a circle system at a 10 L/min fresh gas flow. Umbilical arterial (UA) and umbilical venous (UV) samples were obtained from a loop of umbilical cord, doubly clamped before the baby breathed, and the maternal radial artery sample was collected during uterine incision. Apgar scores were noted at 1 and 5 minutes. Base excess (BE) was assessed by Severinghaus equation (2) for BE at 3 g of hemoglobin. Fetal oxyhemoglobin saturation was calculated from Nelson's equation with corrections for P_{CO_2} and pH shifts. Data were analyzed by Student's *t*-test between the groups and by linear regression.

RESULTS: Hemodynamic data are shown in the Figure. Maternal Pa_{O_2} values were 96 ± 4 (1 SE) in group A, 232 ± 6 in B, 314 ± 10 in C, and 423 ± 6 torr in D ($p < 0.0005$). The corresponding P_{O_2} (UV) values were 28 ± 1, 36 ± 1.5, 41 ± 1.3, and 47 ± 1.2 torr ($p < 0.0005$) and P_{O_2} (UA) 15 ± 0.7, 19 ± 0.8, 21 ± 0.3, and 25 ± 1.8 torr ($p < 0.0005$ A vs B, $p < 0.05$ B vs C, and $p < 0.005$ C vs D). Both UA and UV oxygen contents increased significantly. Both sets of Apgar scores were similar in all groups. BE (UA) values were: −2.6 ± 0.35 in A, 0.27 ± 0.5 in B, 0.1 ± 0.5 in C, and −0.87 ± 0.26 in D ($p < 0.0005$ A vs B, $p < 0.025$ A vs C or D). BE did not differ significantly among hyperoxic groups. BE (UV) values displayed similar changes.

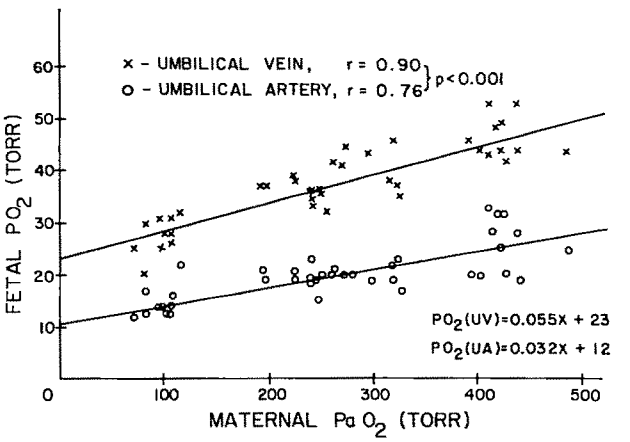


FIGURE. Correlation of maternal Pa_{O_2} with umbilical arterial (UA) and umbilical venous (UV) P_{O_2}.

CONCLUSIONS: Both UV and UA Pa_{O_2} showed a positive correlation with maternal Pa_{O_2} (range 70 to 490 torr). Maternal hyperoxia improves infant acid-base status during cesarean sections under epidural anesthesia.

REFERENCES:
1. Rorke MJ, Davey DA, Du Toit HJ. Foetal oxygenation during caesarean sections. Anaesthesia 1968;23:585-96.
2. Severinghaus JW. Acid-base balance nomogram-A Boston-Copenhagen detente. Anesthesiology 1976;45:539-41.

Blood Flow, Not Low O_2 or pH, Causes Catechol Response to Shock in Lambs

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Cardiovascular collapse, arrest, and hypovolemic shock significantly increase plasma catecholamine levels attributed to the local hypoxemia and acidosis produced by such states. To investigate the relative contribution of hypoxia, acidosis, blood flow, adrenal gland activity, and effects of the central nervous system on the catecholamine response to shock, we studied this response using an in vivo model and artificial circulation.

METHODS: Thirty lambs, 2 to 12 days of age (mean, 5.2 days), were subjected to deep hypothermia (14 C). Each lamb was anesthetized with 1.5% halothane in oxygen and pancuronium. Five animals underwent bilateral adrenalectomy. After a median sternotomy, each lamb was perfused with blood at 100 mk/kg (Bently-Bos oxygenator and Sarns roller

TABLE

Changes in Norepinephrine (NE) and Epinephrine (E) (pg/ml) during Intervention*

	High blood flow	Total circulatory arrest	Cerebral arrest	Body arrest	Adrenalectomy	Low blood flow
NE	−1,749	+9,558	+30†	+3,217†	+1,070	+1,551†
	±1,497	±4,384	±165	±1,980	±310	±767
E	−2,579	+13,636	+180†	+8,272†	+308	+2,072†
	±2,013	±9,829	±242	±5,144	±258	±375

* Values are means ± SE.

† Statistically different ($p \leq 0.01$) from animals undergoing high blood flow.

pump) and cooled to a rectal temperature of 14 C or less. Once this temperature was achieved, five lambs were given high blood flow (100 ml/kg); five, low flow (10 ml/kg); five, total circulatory arrest; five, upper-body arrest (cerebral); and five, lower-body arrest for 1 hour. The five lambs that underwent bilateral adrenalectomy had blood perfused at the rate of 1 ml/kg. We obtained venous blood samples at 37 C control, 14 C preintervention, and 14 C postintervention. Norepinephrine and epinephrine levels were determined using a radioenzymatic assay; lactate and pyruvate concentrations, using enzymatic assay; and pH, P_{CO_2} and P_{O_2} using standard Radiometer blood gas electrodes. Changes in these variables between preintervention and postintervention in each group and postcontrol values were evaluated, as were changes in pH and in lactate and pyruvate concentrations during the intervention period. Results were analyzed using analysis of variance with replication to determine whether differences among the groups were significant

RESULTS: During deep hypothermia, metabolic demands were minimized: no differences in pH, lactate and pyruvate levels, or O_2 saturation occurred between high flow and low flow groups. Adrenalectomized animals had a 38% smaller change in norepinephrine levels and a 90% smaller change in epinephrine levels with the intervention than did intact animals (Table).

DISCUSSION: Deep hypothermia was used to minimize metabolic demands of animals undergoing perfusion with low blood flow. In this study, during deep hypothermia, that goal was met: although groups had similar pH values, changes in blood flow produce marked alterations in plasma catecholamines. High blood flow slightly decreases catecholamine levels, whereas total circulatory arrest massively increases plasma norepinephrine and epinephrine levels. Although lack of blood flow to the head produces no change in norepinephrine or epinephrine levels, lack of blood flow to the body produces significant elevations in both. These findings demonstrate a primary local sympathoadrenal effect to hypoperfusion when metabolic demands are minimized. A reevaluation of the mechanism of the catecholamine response to "shock" must be considered.

Epiglottitis: Clinical Course and Criteria for Extubation

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This study was undertaken to define more precisely the clinical course of acute epiglottitis and to document the resolution of the obstruction caused by the enlarged epiglottis.

METHODS: Twenty-nine cases of epiglottitis were reviewed retrospectively. All cases were managed by a standard treatment plan that included nasotracheal intubation in the operating room, laryngoscopy in the intensive care unit each morning following the day of intubation, and extubation when the epiglottis was reduced in size to 3 to 4 mm in thickness. Information obtained from hospital records was (*a*) duration of intubation ($Time_{intub}$); (*b*) temperature on admission to the intensive care unit and at 12, 24, 36, 48, and 60 hours; (*c*) time until the child became afebrile, i.e., when temperature stayed below 38 C ($Time_{afeb}$). All data are expressed as means ± SEM. $Time_{afeb}$ was compared to $Time_{intub}$ using linear regression analysis.

RESULTS: The mean age of the children was 44 ± 4 months. All children were febrile on admission with a mean temperature of 39.1 ± 1 C. Temperatures following admission were: 12 hours, 37.9 ± 1 C; 24 hours, 37.8 ± 1 C; 36 hours, 37.5 ± 1 C; 48 hours, 37.4 ± 1 C; 60 hours, 37.4 ± 1 C. $Time_{afeb}$ was 39.7 ± 5.4 hours with a range of 5 to 107 hours. Daily examination of the epiglottis showed that in the first 12 hours of treatment there was often little resolution of the airway swelling (Figs 1 and 2). Children were extubated when swelling was reduced to 3 to 4 mm

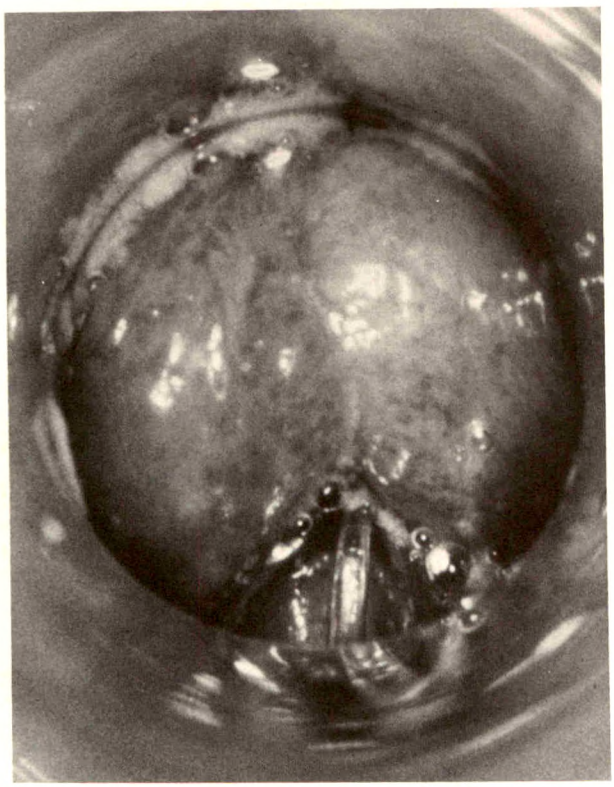


FIG 1. Epiglottis of 4-year-old child immediately after intubation. Endotracheal tube in bottom center of photograph has an external diameter of 7 mm.

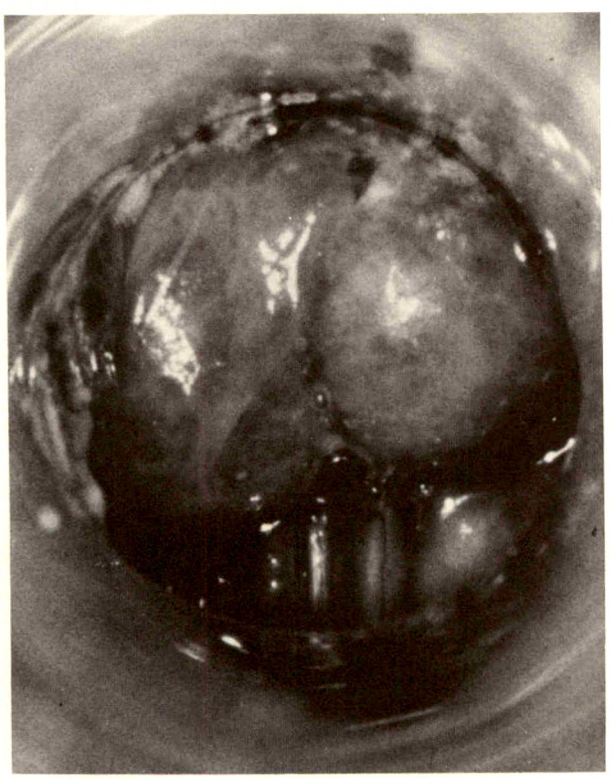


FIG 2. After 12 hours there is almost no change in size of epiglottis.

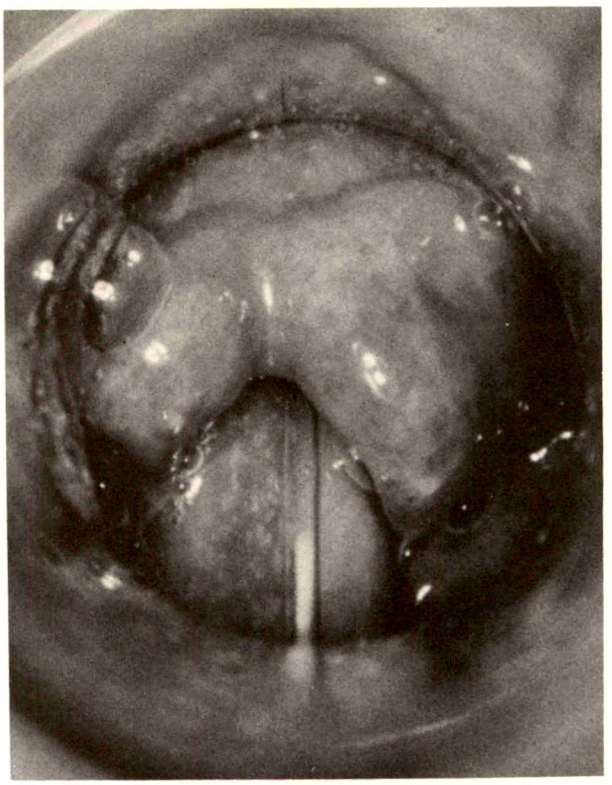


FIG 3. After 36 hours child is ready for extubation.

in thickness (Fig 3). $Time_{intub}$ was 40.6 ± 2.5 hours. There was no correlation between $Time_{afeb}$ and $Time_{intub}$ ($Time_{intub} = 0.13\ Time_{afeb} + 35.4$, $r = 0.27$, NS).

DISCUSSION: Previous reports have provided scanty information on the clinical course of the disease. Published criteria for extubation have included (*a*) regression of toxemia, (*b*) subjective reduction in swelling, and (*c*) extubation after 12 to 14 hours of treatment. This has led to marked variation in $Time_{intub}$ ranging from 12 to 60 hours. The present study has shown that there is no relationship between the febrile nature of the disease and reduction in airway swelling. When our data are compared with the only other individual patient data available (1), which used subjective criteria for extubation, $Time_{intub}$ is significantly reduced from 54.5 to 40.6 hours ($p < 0.01$, unpaired t-test). Reduction in size of the epiglottis during the first 12 hours of treatment may be minimal; we caution against early extubation.

REFERENCE:

1. Oh T, Motoyama EK. Comparison of nasotracheal intubation and tracheostomy in management of acute epiglottitis. Anesthesiology 1975;46:214–6.

Intraoperative Acid-Base Management for the Resection of Thoracoabdominal Aortic Aneurysms: A Comparison of Continuous Infusion of Sodium Bicarbonate versus the Bolus

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Significant systemic acidosis results from the release of the high aortic clamp in patients subjected to thoracoabdominal aneurysm repair without a shunt. The bolus intravenous administration of $NaHCO_3$, frequently used therapeutically in this situation, may produce sudden shifts in pH, P_{CO_2}, and K^+ and ventricular arrhythmias.

This study was designed to measure the efficacy of $NaHCO_3$ infusion during aortic cross-clamping on postclamp changes in pH and K^+, as well as the incidence of arrhythmias in patients having thoracoabdominal aneurysm repair.

Twenty-six patients who were receiving digitalis were studied. Sixteen patients received $NaHCO_3$ (0.05 meq/kg/min) during aortic cross-clamping and 10 patients received bolus injections after the clamp was removed. According to the formula: $NaHCO_3$ dose (meq) = 0.3 × body weight (kg) × base deficit/2, arterial samples were drawn frequently to measure pH, p_{CO_2}, K^+, and base deficit calculation.

The mean aortic clamp times in the $NaHCO_3$ infusion and bolus dose groups were 40 ± 3 and 41 ± 4 minutes, respectively. The mean pH value 10 minutes after aortic unclamping was 7.42 in the infusion group and 7.24 in the group receiving bolus injections. The mean serum K^+ level was 4.0 meq/L before and 4.1 meq/L 10 minutes after aortic unclamping in the infusion group as compared with 3.9 meq/L and 3.5 meq/L after bolus $NaHCO_3$. The mean total $NaHCO_3$ doses for the two groups were 1.9 and 2.9 meq/kg, respectively.

No patient receiving $NaHCO_3$ by infusion developed a ventricular arrhythmia after aortic unclamping. Seven patients treated with bolus doses developed ventricular arrhythmias requiring antiarrhythmic therapy. Six of these patients responded to intravenous lidocaine and one died.

This study presents new information demonstrating the superiority of $NaHCO_3$ infusion during aortic cross-clamping in minimizing postclamp systemic acidosis, hypokalemia, and ventricular arrhythmias.

REFERENCES:
1. Kappagoda CT, Linden RJ, Snow HM. An approach to the problems of acid-base balance. Clin Sci 1970;39:169–82.
2. Schwartz WB, Relman AS. A critique of the parameters used in the evaluation of acid-base balance. N Engl J Med 1963;268: 1382–8.

Plasma Electrolytes and Electrolyte Excretion during Osmotic and Combined Osmotic-Loop Diuresis in Neurosurgery

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Diuretics such as mannitol (M) and furosemide (F) are used in neurosurgery to reduce brain bulk. As M and F act on two different receptor systems, diuresis is enhanced by combining the two drugs. Marked diuresis, however, is accompanied by electrolyte imbalance. The present study compares the effect of osmotic diuresis with osmotic-loop diuresis on plasma electrolyte levels and water and electrolyte excretion.

METHOD: Patients (n = 22) with normal renal functions who were undergoing brain surgery received, in random order, a rapid infusion of M (1.4 g/kg) or M (1.4 g/kg) and F (0.3 mg/kg). Simultaneous arterial blood and urine samples were drawn to measure blood gas tensions, pH, osmolality, Na^+, K^+, Cl^-, and water and electrolyte excretion. The measurements were made at preset intervals before and after diuretic infusion.

RESULTS: Hyponatremia, hypokalemia, hypochloremia, and hyperosmolality were more significant ($p < 0.05$) and prolonged with M and F than with M alone (Table). No electrocardiographic changes were observed. Brain relaxation was considerably greater and more consistent with M and F than with M. This was reflected in the amount of water and ions excreted. During active diuresis H_2O, Na^+, K^+, and Cl^- excretion after M and F was disproportionate to the H_2O and ions loss after M. This magnitude of salt and H_2O excretion leveled off at the end of diuresis (Table).

CONCLUSION: Although optimal brain relaxation is achieved with osmotic-loop diuresis, hyponatremia, hypochloremia, and the persistent osmotic gradient may cause delayed arousal. If M and F therapy is contemplated, plasma osmolality and electrolyte levels must be measured at least at peak and at the end of diuresis. Replacement of Na^+ and Cl^- loss must begin in the operating room.

TABLE

Plasma Electrolyte Levels, Water, and Electrolyte Excretion with Mannitol (M) and Combined Mannitol-Furosemide (M+F) Induced Diuresis*

	Drug	Measurement period (N = 11)					
		Before diuresis	Onset of diuresis	Peak diuresis	Low diuresis	RR-3 hr†	RR-4 h†
Serum values							
Osmolality (mOsm/L)	M	287 ± 2	301 ± 1.5‡	300 ± 2‡	297 ± 2‡	—	—
	M+F	291 ± 3	312 ± 3‡	309 ± 3‡	306 ± 3‡	303 ± 3.5	305 ± 6
Na^+ (meq/L)	M	134 ± 1	129 ± 1‡	131 ± 1‡	131 ± 1‡	—	—
	M+F	138 ± 0.5	124 ± 3‡	124 ± 3‡	129 ± 1‡	131 ± 1.3‡	133 ± 2.0‡
K^+ (meq/L)	M	4.2 ± 0.1	3.9 ± 0.1	4.1 ± 0.1	4.1 ± 0.1	—	—
	M+F	4.4 ± 0.1	3.7 ± 0.2‡	3.7 ± 0.2‡	3.8 ± 0.2‡	3.8 ± 0.2	3.9 ± 0.2‡
Cl^- (meq/L)	M	102 ± 1	99 ± 1	99 ± 1	101 ± 1	—	—
	M+F	102 ± 2	92 ± 2	91 ± 3‡	96 ± 2‡	97 ± 1	99 ± 1
Renal excretion							
Total output (ml)	M	446 ± 116	495 ± 53	451 ± 68	170 ± 28	—	—
	M+F	560 ± 50	860 ± 54	940 ± 30	600 ± 71	365 ± 47	254 ± 32
$U_{H_2O}V$ (ml/min)	M	—	17 ± 1.5	12.6 ± 2.0	3.8 ± 0.4	—	—
	M+F	—	30.3 ± 3.8	42 ± 7	17 ± 3.6	10 ± 2.1	4.6 ± 0.3
$U_{Na}V$ (μeq/min)	M	—	13.09 ± 0.17	7.18 ± 0.16	0.65 ± 0.01	—	—
	M+F	—	81.10 ± 1.5	163.4 ± 6.3	17.2 ± 0.9	4.6 ± 0.2	0.5 ± 0.01
U_KV (μeq/min)	M	—	2.38 ± 0.03	1.64 ± 0.04	0.23 ± 0.01	—	—
	M+F	—	11.51 ± 0.3	14.7 ± 0.35	4.25 ± 0.25	2.0 ± 0.15	6.0 ± 0.34
$U_{Cl}V$ (μeq/min)	M	—	12.24 ± 0.15	7.81 ± 0.18	0.72 ± 0.01	—	—
	M+F	—	87.9 ± 1.6	173.04 ± 5.8	22.1 ± 1.08	6.0 ± 0.34	0.74 ± 0.01

* Serum values are means ± SE. Renal excretion values are means ± SD. N = 11 for each measurement period.
† RR-3 hr, recovery room, 3 hours after onset of diuresis; RR-4 hr, 4 hours after onset of diuresis.
‡ Significantly different from values before diuresis, $p < 0.05$.

Hormonal Effects of Sufentanil Anesthesia

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High dose fentanyl anesthesia has been shown to reduce hormonal "stress" responses during cardiac surgery in the period before cardiopulmonary bypass (1). Sufentanil is a new synthetic opioid analgesic approximately 10 times as potent as fentanyl which produces minimal change in cardiovascular dynamics when used as an opioid anesthetic in man (2). This study was designed to investigate whether sufentanil blocks hormonal responses to surgery and, if so, whether the reduction in stress response is continued during cardiopulmonary bypass and after surgery.

METHOD: Ten consenting adult patients (seven men, three women, aged 46.7 ± 5.35 years, weight 70.6 ± 4.59 kg, having six coronary artery bypass grafts, two valve replacements, and two other operations) undergoing cardiac surgery were studied. Patients for coronary artery surgery were taking beta-blocking drugs, which were discontinued the evening before surgery. Anesthesia technique was as follows: premedication, lorazepam, 4 to 5 mg orally; induction, sufentanil, 12 μg/kg, with pancuronium, 8 mg, for neuromuscular blockade; intubation; ventilation with air/O_2 (F_{IO_2} = 0.5); sufentanil, 3 μg/kg, before skin incision; and sufentanil, 7 μg/kg, before bypass. Blood samples were taken (*a*) before induction, (*b*) after induction, (*c*) after intubation, (*d*) after sternotomy, (*e*) before bypass, (*f*) 15 minutes and (*g*) 60 minutes during bypass, (*h*) 30 minutes after bypass, (*i*) after sternal closure, and (*j*) 1 hour after return to the intensive care unit. Samples were assayed for levels of epinephrine, norepinephrine, dopamine, antidiuretic hormone, cortisol, insulin, prolactin, growth hormone, and glucose. Data are presented as means ± SEM. Statistical analysis was by analysis of variance and difference from control value determined with a modified *t*-test (Bonnferroni).

RESULTS: Epinephrine (control values 99.6 ± 24.15 pg/ml) increased significantly by sample *f* and remained elevated; peak value sample *g*: 1054.3 ± 332.10 pg/ml. Norepinephrine (control values 338.8 ± 54.10 pg/ml) increased significantly by sample *g* and remained elevated; peak value sample *g*: 1939.4 ± 382.67 pg/ml. Dopamine (control values 55.1 ± 10.67 pg/ml) increased significantly by sample *h* and remained elevated; peak value sample *h*: 20,352 ± 10,986.80 pg/ml. Antidiuretic hormone (control values 9.05 ± 1.64 pg/ml) was only significantly elevated at sample *i* (35.5 ± 8.60 pg/ml). Cortisol (control

values 0.383 ± 0.045 μmol/L) level was significantly increased at sample *j* (0.98 ± 0.105 μmol/L). Insulin (control values 11.4 ± 1.54 mU/L) showed no statistically significant changes. Prolactin (control values 16.5 ± 2.87 μg/L) was significantly increased at samples *b* and *c*. Growth hormone (control values 5.65 ± 2.87 mU/L) showed no statistically significant changes. Glucose (control values 5.0 ± 0.20 mmol/L) increased significantly by sample *g* and continued to increase by sample *j* to 9.2 ± 0.40 mmol/L.

DISCUSSION: Fentanyl abolishes catecholamine responses to surgery but not to bypass compared with halothane anesthesia (1). Using sufentanil, a much more potent agent, in doses equivalent to 200 μg/kg of fentanyl does not abolish this catecholamine response. Catecholamine levels remain high after bypass. However, sufentanil is potent at blocking antiduretic hormone responses. The fact that cortisol and glucose concentrations are increased, as well as catecholamines after surgery, suggests that the abolition of the stress response is of limited duration. It may still be valuable in patients with severe coronary artery disease but there is, as yet, no evidence to suggest that the limited abolition of stress response obtained with opioid anesthesia will affect morbidity and/or mortality.

REFERENCES:
1. Sebel PS, Bovill JG, Schellekens APM, Hawker CD. Hormonal responses to high-dose fentanyl anaesthesia. Br J Anaesth (in press 1981).
2. Sebel PS, Bovill JG. Cardiovascular effects of sufentanil anesthesia. Anesth Analg 1982;61:115–8.

Intravenous Nitroglycerin and Myocardial Metabolism during Anesthesia in Patients Undergoing Myocardial Revascularization

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Maintenance of a favorable myocardial oxygen supply/demand ratio is mandatory during anesthesia for cardiac surgery. Intravenous nitroglycerin (IV-NG) is frequently used to control the intraoperative hypertensive response to intubation and sternotomy (1, 2); however, the direct measurement of myocardial metabolism in this setting has not been described. Accordingly, we measured coronary hemodynamics (using a thermodilution coronary sinus catheter) and simultaneous arterial/coronary sinus lactate and O_2 content in eight patients (aged 56 ± 8 years) poststernotomy following IV-NG infusion [total dose 12 ± 8 (SD) μg/kg given over 6 ± 1 minutes]. Before surgery, angiographic ejection fraction = 70% ± 10%, range of diseased coronaries, 1 to 3. Chronic cardiac drugs were propranolol (n = 2) and long-acting nitrates (n = 3). Premedication was with oral secobarbital (mean dose 263 mg) and morphine (0.25 mg/kg IV). Anesthesia was induced either with halothane (1% to 1.5% inspired) for 10 minutes after thiopental (mean dose 133 mg) with halothane (0.5% to 1.0%) for maintenance in six patients, and morphine induction (0.75 mg/kg) with diazepam (mean dose 5 mg) in two patients.

TABLE

Effects of Intravenous Nitroglycerin (12 μg/kg in 6 Minutes)*

	Before IV-NG	After IV-NG	*p*
Heart rate (beats/min)	72 ± 23	70 ± 20	NS
Mean arterial pressure (mm Hg)	106 ± 16	72 ± 13	<0.05
Pulmonary capillary wedge pressure (mm Hg)	21 ± 5	12 ± 3	<0.05
Systemic vascular resistance (dyne·sec·cm^{-5})	1931 ± 688	1090 ± 452	<0.05
Right atrial pressure (mm Hg)	10 ± 2	7 ± 1	<0.05
Cardiac index (L/min/m^2)	2.14 ± 0.6	2.55 ± 0.6	NS
Coronary blood flow (ml/min)	102 ± 43	84 ± 61	NS
Coronary vascular resistance (mm Hg/ml/min)	1.08 ± 0.46	1.08 ± 0.61	NS
Coronary sinus oxygen content (ml/100 ml)	6.3 ± 1.4	7.7 ± 2.0	<0.05
Myocardial oxygen content (ml/min)	10.8 ± 5.8	6.9 ± 4.2	<0.05
Myocardial lactate extraction (%)	22 ± 16	29 ± 12	NS
Rate-pressure product	10,967 ± 3,219	7,015 ± 2,150	<0.05

* Values are means ± SE.

The results before and after sternotomy are shown in the Table. Nitroglycerin significantly decreased the preload (right atrial pressure and pulmonary capillary wedge pressure) and afterload (systemic vascular resistance) with a decrease in mean arterial pressure. This was metabolically well tolerated with a significant increase in coronary sinus-O_2 content resulting in a significant reduction in myocardial oxygen content, as coronary blood flow was unchanged. There was no alteration in myocardial lactate extraction. Left ventricular stroke volume index and stroke work index were unchanged.

We could not examine regional myocardial pathophysiology. We conclude that IV-NG, in large doses, effectively attenuates the hypertensive response to sternotomy in coronary patients, without adverse alterations in global myocardial metabolic state.

REFERENCES:
1. Hempelmann G, Piepenbrock S, Seitz W, et al. Changes in hemodynamic parameters, inotropic state, and myocardial oxygen consumption owing to intravenous application of nitroglycerin. J Thorac Cardiovasc Surg 1977;73:836–47.
2. Stengert KB, Wilsey BL, Hurley EJ, et al. Incremental intravenous nitroglycerin for control of afterload during anesthesia in patients undergoing myocardial revascularization. Anaesthesist 1978;27:223–7.

Transcutaneous Cranial Electrical Stimulation Decreased Narcotic Requirements during Neuroleptanesthesia and Operation in Man

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A recent study has demonstrated that transcutaneous cranial electrical stimulation (TCES) significantly decreases (45% to 50%) the MAC of nitrous oxide in man (1). This suggests that simultaneous use of TCES during clinical anesthesia might decrease patient requirements for inhalation or intravenous analgesics. In this study we evaluated the influence of TCES on fentanyl requirements in 50 patients undergoing a variety of urologic operations with pure neuroleptanesthesia (droperidol, diazepam, fentanyl, and air-oxygen) with (group I) or without (group II) simultaneous TCES.

The patients were premedicated with atropine and diazepam and randomly assigned to group I or II. All patients had silver electrodes (three) applied between the eyebrows and behind each mastoid process and attached to a 167 kHz current generator. Current was delivered only to group I. The wave form was a complex, nonsinusoidal, nonsquare wave pattern that was applied intermittently in a 3-msec-on 10-msec-off sequence. The anesthesiologist was unaware of whether patients were in group I or II. All patients had anesthesia induced with droperidol (10 mg IV), diazepam (15 mg IV), and pancuronium (0.08 mg/kg IV); all were intubated and had anesthesia maintained with 100-μg intravenous increments of fentanyl whenever systolic arterial blood pressure became >20% of control values. Patients breathed 40% oxygen in air. At the end of surgery, muscular relaxation was reversed and patients were immediately extubated.

The operation types and times (123 ± 34 min) were similar in the two groups. Fentanyl requirements averaged 6.1 and 7.9 μg/kg/min for a total dosage of 9.0 and 12.5 μg/kg for the entire operation in groups I and II, respectively. Differences in fentanyl dosage were markedly significant, $p < 0.005$. No patient remembered any aspect of the anesthetic or surgical procedure.

These data indicate that TCES augments the analgesic effects of fentanyl and thus reduces fentanyl requirements during urologic operations with neuroleptanesthesia.

REFERENCE:
1. Stanley TH, Limoge A, Cazalaa JB, et al. Transcutaneous cranial electrical stimulation increases the MAC of N_2O in man. Anesthesiology (in press 1981).

Ketanserin, a Specific 5 HT_2-Receptor Blocker, in Treatment of Postoperative Hypertension following Coronary Artery Bypass Surgery

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Postoperative hypertension following coronary artery bypass surgery is an important problem in intensive care units. Increased levels of catecholamines, renin, and angiotension due to cardiopulmonary bypass, hemodilution, and activation of reflex pressor mechanisms are believed to contribute to this phenomenon (1, 2). The role of 5-hydroxytryptamine (serotonin), released from platelets or other sources, was investigated by injecting ketanserin in patients with developing hypertension after coronary artery bypass surgery.

Intravenous administration of ketanserin was started at intra-arterial systolic blood pressure (SBP) levels of 150 mm Hg or higher. The patients were allocated to three groups. In group I (n = 15) 10 mg of ketanserin was injected as a bolus. In 13 patients a mean decrease in SBP of 23% (range: 14% to 33%) was observed after 5 minutes. Heart rate, central venous pressure, and left atrial pressure did not change significantly. Hence the rate-pressure product decreased significantly (mean decrease: 26%). SBP increased again 30 to 50 minutes after the injection. Two patients did not respond. In group II (n = 15) a 10-mg ketanserin bolus was immediately followed by a continuous infusion of 4 mg/hr for 2½ hours. Five minutes after injection, SBP decreased significantly (mean 19%; range 13% to 35%) and gradually normalized during the infusion (mean 123 mm Hg). Rate-pressure product decreased significantly (mean decrease 19%). No other important changes could be detected. Three patients did not respond in this group. In group III (n = 10) the same procedure was followed as in group II, but in addition a Swan-Ganz thermodilution catheter was inserted through the right internal jugular vein to measure pulmonary capillary

wedge pressure and cardiac output and to calculate systemic vascular resistance. In this group a significant decrease in SBP (mean 20%; range 14% to 29%) and a significant increase in cardiac output (mean 11%; range 0% to 19%) was found 5 minutes after injection in eight patients. Hence systemic vascular resistance decreased significantly (mean 27%; range 12% to 35%). During the continuous infusion SBP and systemic vascular resistance remained at normal levels. The other variables did not change significantly. Two patients did not respond. No rebound effects were noted after stopping the infusions.

The present findings indicate that serotonin plays a role in the majority of patients with postoperative hypertension following coronary artery bypass surgery. The favorable effect of ketanserin is the decrease in systemic vascular resistance, without causing a significant reflex tachycardia, as is seen with vasodilators such as nitroprusside and nitroglycerin.

REFERENCES:
1. Salerno TA, et al. J Thorac Cardiovasc Surg 1981;81:396–9.
2. Estafanous FG, et al. Am J Cardiol 1980;46:685–94.

Halothane-Induced Platelet Dysfunction

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Recent data suggest that halothane may alter platelet function via an effect on adenyl cyclase and increase blood loss during the operative period. To study the effects of anesthetic agents on platelet function in vivo, 27 patients (aged 18 to 60), undergoing elective operative procedures (A.S.A. classification I to III) with minimum risk for blood loss, were sequentially studied as to bleeding time, platelet count, platelet sizing, clottable fibrinogen, and platelet function. Fifteen patients received halothane (1.25 to 2 vol% inspired concentration), six patients received enflurane, and six patients received narcotics (morphine or fentanyl). N_2O (60%) and O_2 were used as supplemental anesthesia with non-depolarizing muscle relaxants added in most cases. Arterial blood gas tensions and central temperature were similar in all patients, and the preoperative fasting fluid decrement was filled in the 1st hour of anesthesia. Hemostatic measurements were performed preoperatively (before and 1 hour after premedication), at hourly intervals during (up to 3 hours), and for 3 hours after anesthesia. No significant differences in platelet sizing or clottable fibrinogen occurred. In comparison with the groups receiving enflurane or narcotics, the group given halothane demonstrated an increase, up to 16 minutes, in the Simplate bleeding time (normal 3 to 8 minutes), at 2 hours into anesthesia, returning to normal by 3 hours after anesthesia. A concurrent mild decrease in the platelet count to 95,000 ± 15,000 mm^3, values inappropriate to account for the prolonged bleeding time, was noted with normalization by 3 hours after anesthesia. Platelet function studies were abnormal in eight of nine patients given halothane, in failure to induce aggregation with sodium arachidonate (0.45 mM). Seven of nine patients had only a single wave reponse to epinephrine (50 μM) and six of nine had a decreased response to collagen. Platelet factor 3 availability was abnormal in two patients. These results indicate that patients undergoing general anesthesia with halothane develop a transient degree of thrombocytopenia and significant platelet dysfunction characterized by a defect in prostaglandin synthesis.

Cardiovascular Effects of Diazepam-Fentanyl Anesthesia in Patients with Coronary Artery Disease

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High dose fentanyl for induction of anesthesia in patients with coronary artery disease has been reported to produce minimal hemodynamic changes. Diazepam also produces minimal cardiovascular changes during induction both in cardiac and noncardiac patients. The purpose of this study was to evaluate the hemodynamic changes produced when diazepam preceded high dose fentanyl anesthesia.

METHODS: Twenty patients scheduled for elective coronary artery surgery were randomly selected for study in four groups. All patients received 50 μg/kg of fentanyl administered at 400 μg/min via a constant infusion pump. In addition, patients in group 2 received diazepam, 0.125 mg/kg; group 3 received 0.25 mg/kg of diazepam, and group 4 received 0.5 mg/kg IV of diazepam before the fentanyl. Patients in group 1 received only fentanyl. Hemodynamic measurements and blood samples for plasma histamine and catecholamine assay were obtained before and after administration of the diazepam, after 25 μg/kg and 50 μg/kg of fentanyl, and at 5 and 10 minutes after the fentanyl.

RESULTS: There were no significant changes in

TABLE

Hemodynamic Data after Administration of Fentanyl with or without Diazepam*

	Control values	After diazepam	Fentanyl		After fentanyl	
			25 μg/kg	50 μg/kg	5 min	10 min
Group 1						
$\overline{BP}$	104 ± 9	—	103 ± 8	103 ± 6	94 ± 5	95 ± 7
CI	2.57 ± 0.2	—	2.54 ± 0.2	2.63 ± 0.1	2.46 ± 0.2	2.27 ± 0.2
SVR	21.1 ± 2	—	21.0 ± 3	19.8 ± 1	20.2 ± 2	21.1 ± 2
Group 2						
$\overline{BP}$	100 ± 5	90 ± 4	77 ± 7†	77 ± 5†	76 ± 8†	74 ± 7†
CI	2.36 ± 0.1	2.11 ± 0.2	2.43 ± 0.2	2.50 ± 0.4	2.40 ± 0.3	2.48 ± 0.2
SVR	20.2 ± 2	19.5 ± 2	14.8 ± 2†	14.6 ± 2†	14.8 ± 2‡	13.6 ± 2‡
Group 3						
$\overline{BP}$	101 ± 5	91 ± 6	61 ± 8‡	75 ± 4†	70 ± 6‡	68 ± 5‡
CI	2.56 ± 0.2	2.35 ± 0.2	2.26 ± 0.2†	2.34 ± 0.2	2.28 ± 0.2	2.06 ± 0.1
SVR	19.5 ± 2	18.4 ± 2	12.8 ± 3†	15.5 ± 2†	14.7 ± 2	15.2 ± 2
Group 4						
$\overline{BP}$	94 ± 9	94 ± 10	64 ± 7‡	69 ± 6‡	73 ± 3‡	70 ± 5‡
CI	2.28 ± 0.1	2.39 ± 0.2	2.13 ± 0.1	2.11 ± 0.1	2.07 ± 0.1	2.01 ± 0.1
SVR	20.8 ± 3	19.4 ± 3	14.9 ± 3‡	16.1 ± 3†	17.2 ± 2†	17.4 ± 3†

* Values are means ± SEM. Abbreviations are: $\overline{BP}$, mean blood pressure (torr); CI, cardiac index (L/min/m^2); SVR, systemic vascular resistance (units).

† $p < 0.05$ compared with control values.

‡ $p < 0.01$ compared with control values.

heart rate, mean pulmonary artery pressure, mean pulmonary capillary wedge pressure, or arterial blood gas tensions throughout the period of the study. Patients who received fentanyl only (group 1) had no significant changes in mean blood pressure, cardiac index, or systemic vascular resistance. Diazepam alone produced no significant changes. Patients who received diazepam before fentanyl (groups 2 to 4) showed significant decreases in mean blood pressure and systemic vascular resistance with fentanyl administration. These data are summarized in the Table. No correlation was found between the hemodynamic changes and the histamine or catecholamine levels.

DISCUSSION: These data confirm that administration of high dose fentanyl alone produces minimal cardiovascular changes. More important, fentanyl produces significant hemodynamic changes when administered after diazepam. Patients in groups 2 to 4 had significant decreases in both mean blood pressure and systemic vascular resistance. The vasodilation as reflected by systemic vascular resistance appears to be maximal after the smallest dose of diazepam. However, larger doses did produce more hypotension suggesting the possibility of a second action. Thus, it appears that prior administration of diazepam interacts with high dose fentanyl to produce its undesirable effects on the peripheral vasculature and perhaps the myocardium. The exact mechanism of this action is unclear but neither catecholamines nor histamine release appear to be involved.

Nifedipine and Halothane Interaction: Hemodynamic Depression in Dogs

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Nifedipine is a calcium (Ca^{2+}) channel blocker used for treatment of coronary spasm, angina pectoris, hypertension, obstructive myocardiopathy, and myocardial protection. Halothane has some Ca^{2+} inhibition actions, and it shares with nifedipine negative inotropic and vasodilation properties. Many patients will receive both drugs; therefore, we have investigated the interaction of nifedipine and halothane.

METHODS: In six mongrel dogs, anesthesia was induced with thiopental and maintained with halothane in oxygen. Instrumentation consisted of catheters (for arterial, left atrial, and left ventricular pressures), flow probes (for pulmonary artery and left anterior descending coronary artery), electrocardiogram (lead II), and contractile force (strain gauge arch). The dP/dt_{max} and mean blood pressure were measured electronically. The experimental plan was

TABLE

Values during Administration of Halothane Anesthesia and Nifedipine*

	1% H	1% H + N	2% H	2% H + N
HR (beats/min)	140 ± 10.2	137 ± 6.3	125 ± 8.2†	123 ± 6.0†
SBP (mm Hg)	128 ± 4.6	115 ± 7.9	93 ± 9.8§	95 ± 12.6§
DBP (mm Hg)	77 ± 4.3	68 ± 6.4	55 ± 6.4§	56 ± 8.5§
MBP (mm Hg)	90 ± 4.8	83 ± 6.4	65 ± 7.1§	68 ± 9.1§
LAP (mm Hg)	9.3 ± 0.92	9.3 ± 1.02	8.8 ± 0.95	9.8 ± 1.1
QPA (L/min)	4.1 ± 0.40	3.3 ± 0.51	2.7 ± 0.49†	2.5 ± 0.63†
QLAD (ml/min)	39 ± 8.3	35 ± 3.1	19 ± 1.3†	23 ± 4.3†
dP/dt_{max}	2715 ± 436.4	2200 ± 386.7	1550 ± 282.7‡	1346 ± 346.7‡
CF	16 ± 4.4	17 ± 3.2	14 ± 3.2	14 ± 2.4

* Values are means ± SEM. Abbreviations used are: 1% H, 1% halothane; 1% H + N, halothane 30 minutes after nifedipine, 10 to 15 μg/kg; 2% H, 2% halothane; 2% H + N, halothane 30 minutes after nifedipine, 10 to 15 μg/kg; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; LAP, left atrial pressure; QPA, pulmonary artery blood (i.e., cardiac output); QLAD, left coronary artery flow; and CF, contractile force (mm excursion).

† $p < 0.05$ different from 1% H and 1% H + N.

‡ $p < 0.002$ different from 1% H and 1% H + N.

§ $p < 0.001$ different from 1% H and 1% H + N.

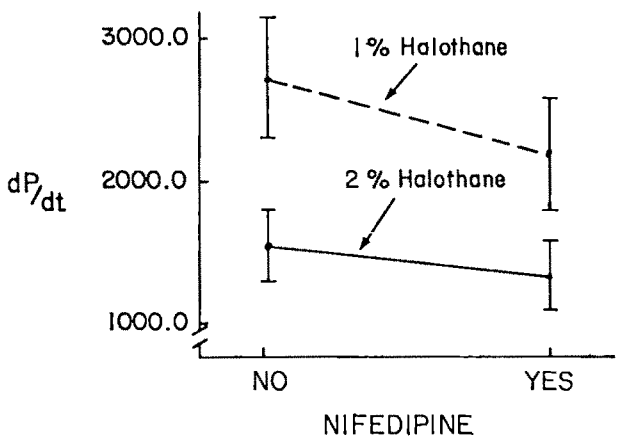


FIGURE. dP/dt_{max} (mm Hg/sec) at steady-state 1% and 2% halothane before (NO) and 30 minutes after (YES) administration of nifedipine, 10 to 15 μg/kg. Halothane significantly ($p < 0.002$) depressed dP/dt, but nifedipine decreases are not statistically significant. Note that slope of second curve is flatter than first indicating that increase in halothane concentration does not increase danger of unexpected decrease in contractile force due to addition of nifedipine.

random administration of nifedipine, 10 to 15 μg/kg IV, (over 2 minutes) before or after steady-state 1% or 2% halothane. After 30 minutes at each of the four conditions, measurements were made. Arterial blood gas tensions, temperature, left atrial pressure, and acid-base status were kept constant. Analysis of variance was used to determine significant differences between mean values at each measurement point.

RESULTS: The Table contains the results. Statistical analysis revealed that administration of nifedipine (30 minutes after administration) had no significant effect on any variable, whereas increasing the dose of halothane significantly ($p < 0.05$) decreased heart rate, blood pressure, cardiac output, and dP/dt_{max}. Tests to determine whether addition of nifedipine altered the slope of each halothane concentration variable (Figure) revealed the tendency for the second curve (2% halothane) to be flatter than the first (1% halothane), but the slopes were not significantly different.

CONCLUSION: These data demonstrate that nifedipine given during halothane anesthesia does not produce any significant decrease in myocardial contractility. There are two potential clinical situations in which inhalation anesthetic drugs and Ca^{2+} blockers will interact: first, anesthetizing patients taking Ca^{2+} blockers and, second, giving the Ca^{2+} blocker to anesthetized patients. We have investigated the latter, but our data show that there is no potentiation of the negative inotropic effect of halothane.

Preadmission Testing: It Can Make a Difference!

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Preadmission testing (PAT) has existed since the 1960s with studies supporting cost effectiveness and decreased length of stay. Our institution offers several PAT packages and availability of many tests on an outpatient basis. Certain criteria have been established to determine which PAT is chosen for elective surgical candidates. The purpose of our study was multifaceted.

METHOD: The results of 500 PAT examinations were recorded and analyzed by the same observer. Particular notations were made when presurgical corrections, cancellation, or medical clearance were deemed necessary. In addition, the surgical staff and a patient group were surveyed regarding awareness, understanding, utilization, and criticism of PAT. Interviews were conducted with various nonphysician hospital staff regarding PAT.

RESULTS: Fifty percent of PAT patients had an abnormality. The vast majority of abnormalities were clinically insignificant regarding anesthetic risks. The highest incidence of significant abnormalities were: (*a*) abnormal serum potassium, 24% (12/50); (*b*) electrocardiograms requiring preoperative medical clearance. Several patients required preoperative cancellation, but no PAT patient reached the operating room and had surgery cancelled for abnormal (missing) laboratory data or medical clearance. Surgeons supported PAT utilization; patients did not particularly understand the benefit of PAT but were receptive; and ancillary staff found PAT effective from a cost and staffing point of view.

DISCUSSION: From an anesthetic viewpoint we found that PAT prevented last minute surgical delays, allowing more efficient operating room utilization. PAT electrocardiograms allowed time for the cardiologist's interpretation and comparison with previous electrocardiograms. The most important cirticism of PAT was the delay in sending laboratory results to the admitting physician before admission. Overall, it is felt that the use of PAT maximized the quality and efficiency of care from the patients' and physicians' perspective.

Duration of Efficacy of Sodium Citrate as an Antacid

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Sodium citrate has recently been shown to be an effective antacid when administered before induction of anesthesia (1). However, the duration of this antacid effect of sodium citrate in surgical patients has not been studied. We undertook a study to determine the duration of antacid effect of sodium citrate when administered as a single dose before induction of anesthesia in 10 patients who were scheduled to undergo elective nongastric surgery.

METHODS: Ten minutes before induction of anesthesia, 10 patients undergoing nongastric surgery received 15 ml of 0.3 M sodium citrate. The patients had been given narcotics as premedicants. Following induction and intubation, an 18-gauge Salem Sump tube was placed through the mouth in each patient. Five milliliters of gastric fluid was aspirated at 15 minutes, 1 hour, and 3 hours following ingestion of sodium citrate. Following each aspiration of the gastric sample the nasogastric tube was cleared of gastric fluid by injection of 5 ml of air. The pH values of all the samples were determined using the pH meter (Orion Research model 301).

TABLE

pH Values of Gastric Samples after Ingestion of Sodium Citrate

Time of sample		
15 minutes	1 hour	3 hours
6.4	6.2	6.2
6.2	5.8	6.2
7.4	6.3	6.4
7.0	7.1	7.2
4.5	4.4	4.2
6.6	7.2	5.0
6.0	6.1	6.2
6.2	5.8	5.8
6.7	6.6	6.8
3.4	2.8	2.8
6.04 ± 1.20*	5.83 ± 1.32*	5.68 ± 1.33*

* Mean ± SD.

RESULTS: The mean pH of the gastric samples taken from 10 patients at 15 minutes, 1 hour, and 3 hours following ingestion of sodium citrate were 6.04, 5.83, and 5.68, respectively. The pH values of the gastric samples of individual patients are given in the Table.

DISCUSSION: Patients undergoing surgery with general anesthesia are at risk of developing lung damage from pulmonary aspiration of low pH (<2.5) (2) acid gastric contents at the time of intubation and extubation. The results of our study indicate that a single-dose administration of sodium citrate maintains the elevated gastric pH for a period lasting at least 3 hours. Our review of surgery records indicates that most of the surgical procedures are accomplished within 3 hours.

REFERENCES:

1. Foulkes E, Jenkins LC. A comparative evaluation of cimetidine and sodium citrate to decrease gastric acidity: effectiveness at the time of induction of anaesthesia. Can Anaesth Soc J 1981;28: 29–32.
2. Mendelson CL. The aspiration of stomach contents into the lungs during obstetrical anesthesia. Am J Obstet Gynecol 1946;52:191.

Chronic Hypokalemia Does Not Increase Anesthetic Dysrhythmias

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In order to determine whether hypokalemia increases the risk of dysrhythmias during anesthesia and surgery, we studied chronically hypokalemic patients who received no potassium replacement before surgery.

METHODS: A prospective study was conducted on 73 adult surgical patients who had serum potassium determinations and a 12-lead electrocardiogram (ECG) performed before surgery. No patient received any potassium replacement before or during surgery, or immediately after surgery. Patients thought to be acutely hypokalemic were excluded from this study. The anesthetic technique was not standardized; management was conducted without any special consideration for the potassium level. During surgery, all patients had continuous lead II ECG monitoring by a trained observer. Any dysrhythmia was recorded on a strip recorder.

After surgery, without knowledge of the potassium levels, we reviewed all dysrhythmic ECG strips and anesthetic charts. The types of rhythms and the necessity for treatment were listed, then the patients were divided into three groups: normokalemia (5.0 to 3.5 meq/L), moderate hypokalemia (3.4 to 3.0 meq/L), and severe hypokalemia (less than 3.0 meq/L). Chi-square tests were performed to compare the characteristics of each group (age, sex, anesthetic agent, location of surgery, preexisting dysrhythmias, A.S.A. risk). Chi-square tests were also used to determine whether any group had a higher incidence of dysrhythmias.

RESULTS: The groups were similiar in all characteristics tested. Junctional rhythms were the most common intraoperative dysrhythmias. There was no difference in the incidence of dysrhythmias in any group (Table).

DISCUSSION: This study gives evidence that patients with chronic hypokalemia do not have an increased incidence of dysrhythmias during anesthesia. Such a result suggests that current practices of acute potassium replacement or surgical postponement may be invalid.

TABLE

Incidence of Intraoperative Dysrhythmias*

Intraoperative rhythm	Normokalemia (N = 38)	Moderate hypokalemia (N = 25)	Severe hypokalemia (N = 10)
		%	
Sinus only	45 ± 8 (N = 17)	48 ± 10 (N = 12)	70 ± 15 (N = 7)
Junctional	21 ± 7 (N = 10)	28 ± 9 (N = 7)	10 ± 9 (N = 1)
PVCs	29 ± 7 (N = 11)	20 ± 8 (N = 5)	10 ± 9 (N = 1)
PACs	13 ± 6 (N = 5)	12 ± 7 (N = 3)	10 ± 9 (N = 1)
Sinus tachycardia	18 ± 6 (N = 7)	4 ± 4 (N = 1)	None observed

* Values are means ± SE. Abbreviations used are: PVC, premature ventricular contraction, PAC, premature arterial contraction.

Usefulness of Pulmonary Artery Catheters during Aortocoronary Bypass Surgery

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Pulmonary artery catheter (PAC) use during aortocoronary bypass (ACB) surgery is controversial. Mangano (1) considered PACs unnecessary in patients with good left ventricular function because of a high correlation between pulmonary capillary wedge pressure (PCWP) and central venous pressure (CVP). Lowenstein and Teplick (2) questioned this conclusion. We prospectively determined the incidence and type of hemodynamic changes missed by experienced cardiac anesthesiologists not using a PAC during ACB.

METHODS: Fifteen patients with multivessel coronary artery disease and good left ventricular function (ejection fraction > 0.5, no dyskinesis) were studied. Radial and pulmonary artery catheters were inserted before anesthetic induction. Diazepam, morphine or fentanyl, pancuronium, nitrous oxide/oxygen, and enflurane, plus indicated cardioactive drugs were administered by a staff anesthesiologist who monitored blood pressure, CVP, electrocardiogram, and clinical signs, but was "blinded" to PAC pressures, cardiac output, and derived indices continuously recorded by another anesthesiologist. Abnormalities in PAC variables were classified as moderate or severe (Table). The "blinded" anesthesiologist was notified of severe abnormalities and the patient was treated appropriately. Linear regression analysis was used to compare the CVP and PCWP.

RESULTS: Abnormal PAC variables occurred in 87% of patients; 34% occurred before intubation and 54% before skin incision. The incidence of PAC ab-

TABLE

Definitions and Occurrences of Moderate and Severe PAC Abnormalities*

	Moderate	Severe
Definitions		
PCWP (mm Hg)	>15	>20
PCWP "V" waves (mm Hg)	>20	>25
CI (L/min/m^2)	<2.0	<1.5
SVR (dynes·sec·cm^{-5})	>2000	>2500
Occurrences		
No. of patients with IAC-ABN	13/15	8/15
No. of PAC-ABN/patient ($\bar{X} \pm$ SD)	6 ± 5	4 ± 4
Total no. of PAC-ABN	73	28
No. of preincision PAC-ABN	40	15

* Abbreviations used are: PAC, pulmonary artery catheter; PCWP, pulmonary capillary wedge pressure; CI, cardiac index; SVR, systemic vascular resistance; PAC-ABN, PAC abnormalities.

normalities is shown in the Table. Eight patients (53%) experienced at least one severe abnormality. The "blinded" anesthesiologist was unaware of any problem during 18 of 28 (65%) severe abnormalities. Nine patients had poor correlation between PCWP and CVP ($r < 0.6$); only one patient had good correlation ($r > 0.8$).

DISCUSSION: These data suggest that during routine ACB, CVP does not predict PCWP in many patients with good left ventricular function. Even before intubation and incision, severe abnormalities in PCWP, cardiac index, and systemic vascular resistance were missed by experienced cardiac anesthesiologists. Therefore, we conclude that preinduction insertion of PACs is justified in the majority of patients undergoing ACB.

REFERENCES:
1. Mangano DT. Monitoring pulmonary arterial pressure in coronary-artery disease. Anesthesiology 1980;53:364-70.
2. Lowenstein E, Teplick R. To (PA) catheterize or not to (PA) catheterize—that is the question. Anesthesiology 1980;53: 361-3.

High-Frequency Jet Ventilation Operational Guidelines

Waterson CK, Calkins JM, Quan SF, Otto CW, and Hameroff SR—University of Arizona Health Sciences Center, Tucson, Arizona

High-frequency jet ventilation (HFJV) is potentially useful for a variety of operating room and intensive care applications (1, 2), but little has been written about how to apply HFJV in a safe and effective manner. This paper summarizes findings regarding the potentially useful operational factors of jet introduction site, inspiratory-expiratory time and resistance ratios, airway pressures, and frequency.

METHODS: Studies were performed in normal anesthetized mongrel dogs (8 to 30 kg) and in two infants in a state of respiratory failure. In the dogs, a solenoid valve was used. In the infants, HFJV was provided by a fluidic system. Both systems periodically pulsed a jet (1 to 30 psi) that was delivered within the endotracheal tube via a catheter or extra lumen (0.8 mm to 3.0 mm i.d.).

RESULTS AND DISCUSSION: The jet is most efficient when introduced as low in the airway as possible. Tracheal trauma due to catheter whip or jet energy has not been noted in our studies. The jet lumen should be small relative to the size of the endotracheal lumen so as to minimize expiratory resistance and avoid excessive positive end-expiratory pressure (PEEP) which may impair CO_2 transport. An inspiratory lumen area:expiratory area ratio of from 1:11 to 1:6 produced adequate ventilation. Some PEEP ($\geq$2 cm H_2O) is necessary to prevent airway collapse at rates too fast and volumes too small to open them during each respiratory cycle. Hypercapnia and hypoxemia have been noted when no PEEP is used. Although airway pressures are low compared with conventional ventilation, airway pressure differences of 5 to 10 cm H_2O are necessary for adequate ventilation (vs >20 cm H_2O in conventional ventilation). Wave forms with rapid pressure increase (flow acceleration) give more effective CO_2 removal than damped wave forms (Pa_{CO_2} = 43.2 vs 84 mm Hg at I/E = 0.43, F = 180 breaths/min). Pa_{CO_2} was lower with I/E time ratio of >0.3 (63.7 mm Hg at I/E = 0.11 vs 30.1 mm Hg at I/E = 0.35, F = 120 breaths/min). Optimum ventilation was achieved with frequencies from 120 to 240 min^{-1} with I/E > 0.3, PEEP $\geq$ 2 cm H_2O, and peak pressures >6 cm H_2O.

CONCLUSIONS: Potentially useful factors in determining the effectiveness of HFJV have been described. The effect of these factors relative to different types of pulmonary pathology have yet to be determined.

REFERENCES:
1. Sjöstrand U, Eriksson I. High rates and low volumes in mechanical ventilation—not just a matter of ventilatory frequency. Anesth Analg 1980;5:567-76.
2. Klain M, Smith RB. High frequency percutaneous transtracheal jet ventilation. Crit Care Med 1977;5:280-7.

Anesthesia Does Not Increase Cerebrospinal Fluid Opioid Peptides in Humans

Way WL, Hosobuchi Y, Eger EI, and Johnson BH—University of California, San Francisco, School of Medicine, San Francisco

Arndt and Frye (1) found that perfusion of the fourth ventricle with naloxone increased blood pressure and wakefulness in halothane-anesthetized dogs. These data suggested that anesthesia may be due to release of endogeneous opioid peptides such as beta endorphin (BE). The present study examines whether thiopental-nitrous oxide-halothane anesthesia increases human cerebrospinal fluid (CSF) BE.

METHODS: Our six patients had undergone preliminary electrode implantation in periaqueductal gray matter for pain treatment. A concomitantly placed ventricular cannula and Ommaya ventricular (CSF) reservoir permitted percutaneous withdrawal of CSF samples. We studied these patients when they subsequently underwent permanent electrode implantation. Our Institutional Committee on Human Research approved the study protocol and consent procedures. No narcotic or electrode stimulation was used for 24 hours before surgery. Immediately before anesthesia 2 ml of CSF was taken. A second sample was obtained 5 minutes after induction with 2 to 5 mg/kg of thiopental plus 70% nitrous oxide. Halothane was then added to allow endotracheal intubation. After 10 additional minutes (just before incision) a third sample was taken. Subsequent samples were drawn 5, 15, and 60 minutes after incision. CSF BE was determined by radioimmunoassay.

RESULTS: Mean values (±SEM) for CSF BE (pg/100 μl) were as follows: control, 69.5 ± 15.1; 5 minutes after induction, 61.2 ± 13.3; after addition of halothane, 61.6 ± 10.8; 5 minutes after incision, 47.2 ± 7.1; 15 minutes after incision, 35.8 ± 3.8; and 60 minutes after incision, 51.0 ± 9.4.

DISCUSSION: Anesthesia or anesthesia plus surgery did not increase BE, suggesting that BE release does not contribute to the anesthesia produced by thiopental, nitrous oxide, or halothane. These data do not exclude a sensitization of opioid receptors as a cause of anesthesia, nor do they exclude other mechanisms of pain attenuation not involving the endorphine systems. Thus the involvement of endorphins in the production of general anesthesia remains debatable; however, we conclude that anesthesia does not require their release in humans.

REFERENCE:
1. Arndt JO, Freye E: Perfusion of naloxone through the fourth cerebral ventricle reverses the circulatory and hypnotic effects of halothane in dogs. Anesthesiology 1979;51:58–63.

Intraoperative Monitoring of Arterial P_{CO_2}: Comparing End-Tidal and Transcutaneous Sensors

Westenskow DR, Jordan WS, and Pace NL—University of Utah College of Medicine, Salt Lake City, Utah

Two noninvasive methods of monitoring Pa_{CO_2}—end-tidal P_{CO_2} measurement in expired gas, and transcutaneous P_{CO_2} using a heated skin surface probe—are compared.

METHODS: Twenty-nine patients (aged 4 to 56 years) were studied during general anesthesia. End-tidal P_{CO_2} was monitored using an Instrumentation Lab 200 infrared analyzer. Transcutaneous P_{CO_2} was measured using a Novametrix analyzer with a heated sensor (44 C) placed immediately below the clavicle. Arterial blood samples were drawn periodically and analyzed using a Radiometer ABL-1 or ABL-2 system.

RESULTS: A total of 127 simultaneous samples of end-tidal P_{CO_2}, transcutaneous P_{CO_2}, and arterial blood were taken. The arterial blood gas samples had a mean Pa_{CO_2} of 36.1 ± 7.5 (SD) torr. The mean end-tidal P_{CO_2} equaled 34.7 ± 6.6 torr. The mean transcutaneous reading was 58.0 ± 13.0 torr. The correlation coefficient between Pa_{CO_2} and end-tidal P_{CO_2} was 0.82 and between Pa_{CO_2} and transcutaneous P_{CO_2}, 0.73. Linear regression analysis gave the relationships end-tidal $P_{CO_2} = 0.72 \times Pa_{CO_2} + 8.56$ (SD from regression = 3.81 torr) and transcutaneous $P_{CO_2} = 1.26 \times Pa_{CO_2} + 12.5$ (SD from regression = 8.7 torr).

CONCLUSION: End-tidal CO_2 monitoring was shown to give an absolute reading that is close to Pa_{CO_2} and has good correlation with Pa_{CO_2}. Transcutaneous P_{CO_2} monitoring is not yet well understood. Our data in adults suggest a correlation between Pa_{CO_2} and the transcutaneous P_{CO_2} even though the absolute transcutaneous reading is significantly different from Pa_{CO_2}. It does appear that trends in Pa_{CO_2} can be followed using transcutaneous monitoring.

This work was supported by the Shriners Childrens Hospital and Novametrix Medical System, Inc.

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7. Agency Publication

   National Center for Health Statistics. Acute conditions: incidence and associated disability, United States July 1968–June 1969. Rockville, Md.: National Center for Health Statistics, 1972. (Vital and health statistics. Series 10: Data from the National Health Survey, no. 69) (DHEW publication no. (HSM)72–1036).

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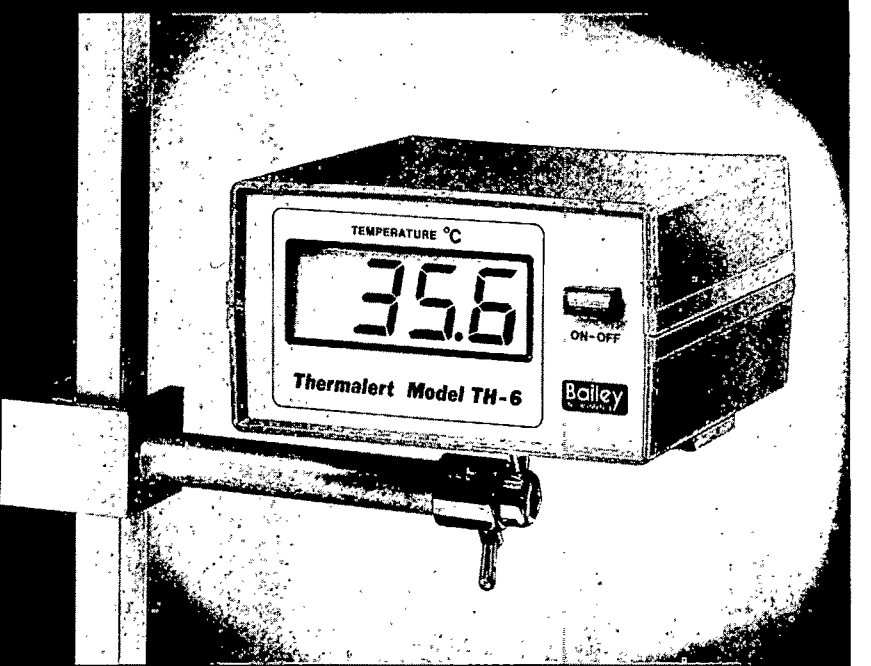
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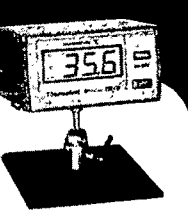
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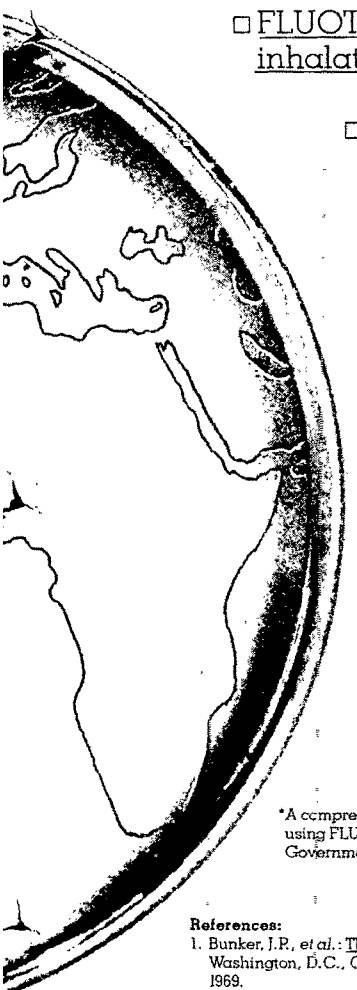
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*A comprehensive retrospective analysis covering 856,000 general anesthesias—nearly one-third using FLUOTHANE. Bunker, J.P., *et al.*: The National Halothane Study. Washington, D.C., Government Printing Office, 1969.

References:

1. Bunker, J.P., *et al.*: The National Halothane Study. Washington, D.C., Government Printing Office, 1969.
2. Brown, B.R., Sipes, I.G.: Biochem. Pharmacol. 26:2091-2094, 1977.
3. Steward, D.J.: Anesthesiology 43:268-276 (Aug.) 1975.
4. Proceedings, Virginia Society of Anesthesiologists, April 20-22, 1979, Richmond, VA.

See following page for Brief Summary.

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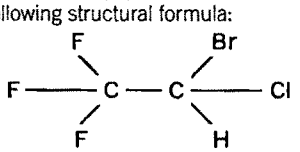
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Description. FLUOTHANE, brand of halothane, U.S.P., is an inhalation anesthetic. It is 2-bromo-2-chloro-1, 1, 1-trifluoroethane and has the following structural formula:



The specific gravity is 1.872-1.877 at 20°C, and the boiling point (range) is 49°C – 51°C at 760 mm Hg. The vapor pressure is 243 mm Hg at 20°C. The blood/gas coefficient is 2.5 at 37°C, and the olive oil/water coefficient is 220 at 37°C. Vapor concentrations within anesthetic range are nonirritating and have a pleasant odor. FLUOTHANE is nonflammable, and its vapors mixed with oxygen in proportions from 0.5 to 50 per cent (v/v) are not explosive.

FLUOTHANE does not decompose in contact with warm soda lime. When moisture is present, the vapor attacks aluminum, brass, and lead, but not copper. Rubber, some plastics, and similar materials are soluble in FLUOTHANE; such materials will deteriorate rapidly in contact with FLUOTHANE vapor or liquid. Stability of FLUOTHANE is maintained by the addition of 0.01 per cent thymol (w/w), up to 0.00025% ammonia (w/w), and storage is in amber colored bottles.

FLUOTHANE should not be kept indefinitely in vaporizer bottles not specifically designed for its use. Thymol does not volatilize along with FLUOTHANE, and therefore accumulates in the vaporizer, and may, in time, impart a yellow color to the remaining liquid or to wicks in vaporizers. The development of such discoloration may be used as an indicator that the vaporizer should be drained and cleaned, and the discolored FLUOTHANE (halothane, U.S.P.) discarded. Accumulation of thymol may be removed by washing with diethyl ether. After cleaning a wick or vaporizer, make certain all diethyl ether has been removed before reusing the equipment to avoid introducing ether into the system.

Actions. FLUOTHANE is an inhalation anesthetic. Induction and recovery are rapid and depth of anesthesia can be rapidly altered. FLUOTHANE progressively depresses respiration. There may be tachypnea with reduced tidal volume and alveolar ventilation. FLUOTHANE is not an irritant to the respiratory tract, and no increase in salivary or bronchial secretions ordinarily occurs. Pharyngeal and laryngeal reflexes are rapidly obtunded. It causes bronchodilation. Hypoxia, acidosis, or apnea may develop during deep anesthesia.

FLUOTHANE reduces the blood pressure, and frequently decreases the pulse rate. The greater the concentration of the drug, the more evident these changes become. Atropine may reverse the bradycardia. FLUOTHANE does not cause the release of catecholamines from adrenergic stores. FLUOTHANE also causes dilation of the vessels of the skin and skeletal muscles.

Cardiac arrhythmias may occur during FLUOTHANE anesthesia. These include nodal rhythm, AV dissociation, ventricular extrasystoles and asystole. FLUOTHANE sensitizes the myocardial conduction system to the action of epinephrine and norepinephrine, and the combination may cause serious cardiac arrhythmias. FLUOTHANE increases cerebral spinal fluid pressure. FLUOTHANE produces moderate muscular relaxation. Muscle relaxants are used as adjuncts in order to maintain lighter levels of anesthesia. FLUOTHANE augments the action of nondepolarizing relaxants and ganglionic blocking agents. FLUOTHANE is a potent uterine relaxant.

Indications. FLUOTHANE (halothane, U.S.P.) is indicated for the induction and maintenance of general anesthesia.

Contraindications. FLUOTHANE is not recommended for obstetrical anesthesia except when uterine relaxation is required.

Warnings. When previous exposure to FLUOTHANE was followed by unexplained jaundice, consideration should be given to the use of other agents.

FLUOTHANE should be used in vaporizers that permit a reasonable approximation of output, and preferably of the calibrated type. The vaporizer should be placed out of circuit in closed circuit rebreathing systems; otherwise overdosage is difficult to avoid. The patient should be closely observed for signs of overdosage, *i.e.*, depression of blood pressure, pulse rate, and ventilation, particularly during assisted or controlled ventilation.

Usage in Pregnancy. Safe use of FLUOTHANE has not been established with respect to possible adverse effects upon fetal development. Therefore, FLUOTHANE should not be used in women where pregnancy is possible and particularly during early pregnancy, unless, in the judgment of the physician, the potential benefits outweigh the unknown hazards to the fetus.

Precautions. The uterine relaxation obtained with FLUOTHANE, unless carefully controlled, may fail to respond to ergot derivatives and oxytocic posterior pituitary extract.

FLUOTHANE increases cerebrospinal fluid pressure. Therefore, in patients with markedly raised intracranial pressure, if FLUOTHANE is indicated, administration should be preceded by measures ordinarily used to reduce cerebrospinal fluid pressure. Ventilation should be carefully assessed, and it may be necessary to assist or control ventilation to insure adequate oxygenation and carbon dioxide removal.

Epinephrine or norepinephrine should be employed cautiously, if at all, during FLUOTHANE (halothane, U.S.P.) anesthesia since their simultaneous use may induce ventricular tachycardia or fibrillation.

Nondepolarizing relaxants and ganglionic blocking agents should be administered cautiously, since their actions are augmented by FLUOTHANE.

It has been reported that in genetically susceptible individuals, the use of general anesthetics and the muscle relaxant, succinylcholine, may trigger a syndrome known as malignant hyperthermic crisis. Monitoring temperature during surgery will aid in early recognition of this syndrome. Dantrolene sodium and supportive measures are generally indicated in the management of malignant hyperthermia.

Adverse Reactions. The following adverse reactions have been reported: mild, moderate and severe hepatic dysfunction (including hepatic necrosis), cardiac arrest, hypotension, respiratory arrest, cardiac arrhythmias, hyperpyrexia, shivering, nausea, and emesis.

Dosage and Administration. FLUOTHANE may be administered by the nonrebreathing technic, partial rebreathing, or closed technic. The induction dose varies from patient to patient. The maintenance dose varies from 0.5 per cent to 1.5 per cent.

FLUOTHANE may be administered with either oxygen or a mixture of oxygen and nitrous oxide.

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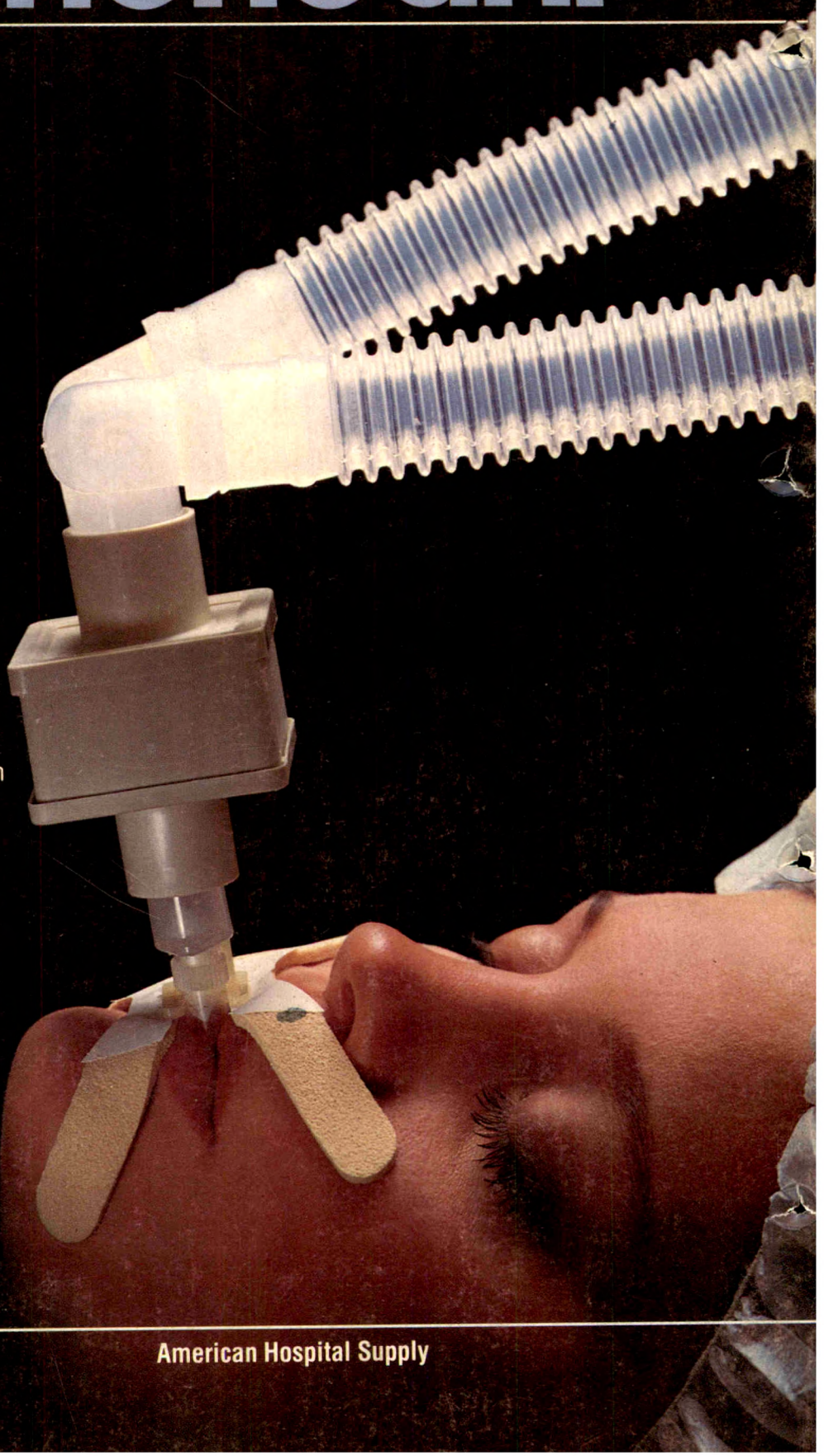
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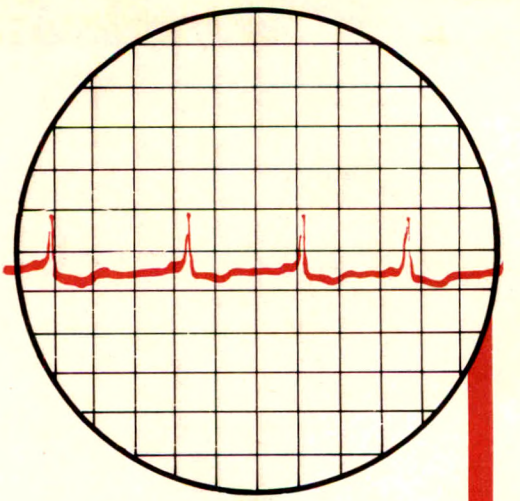
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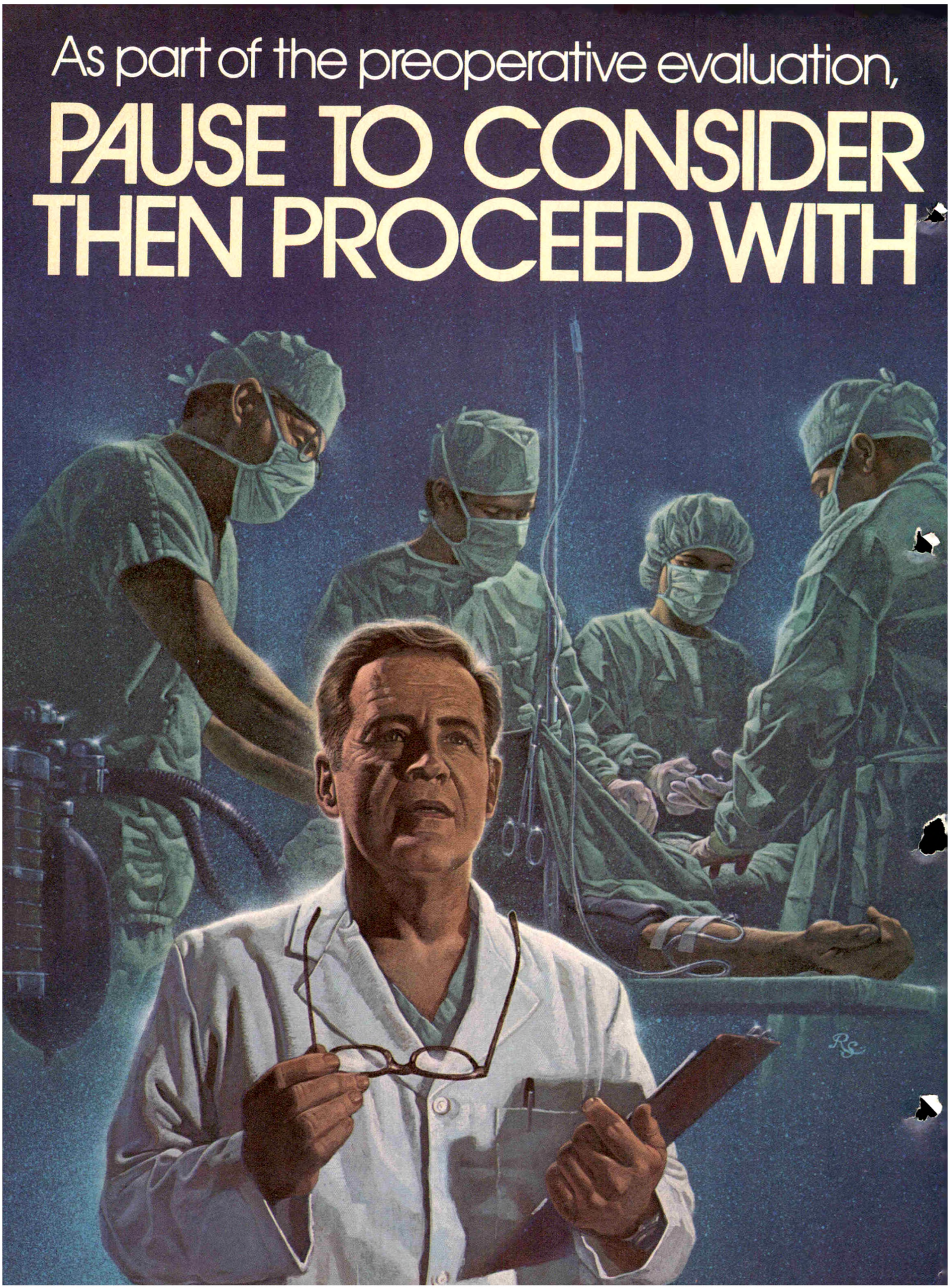
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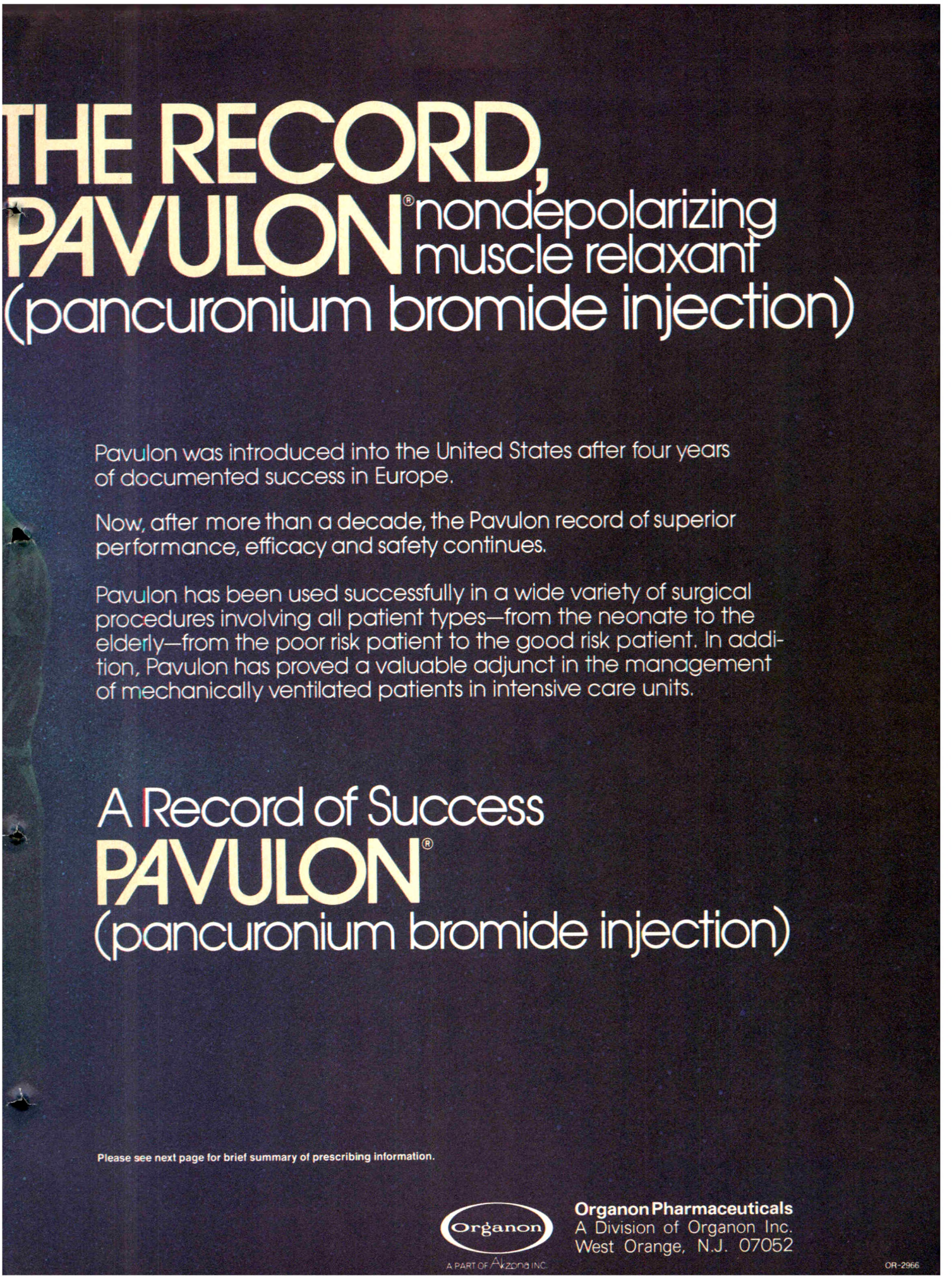
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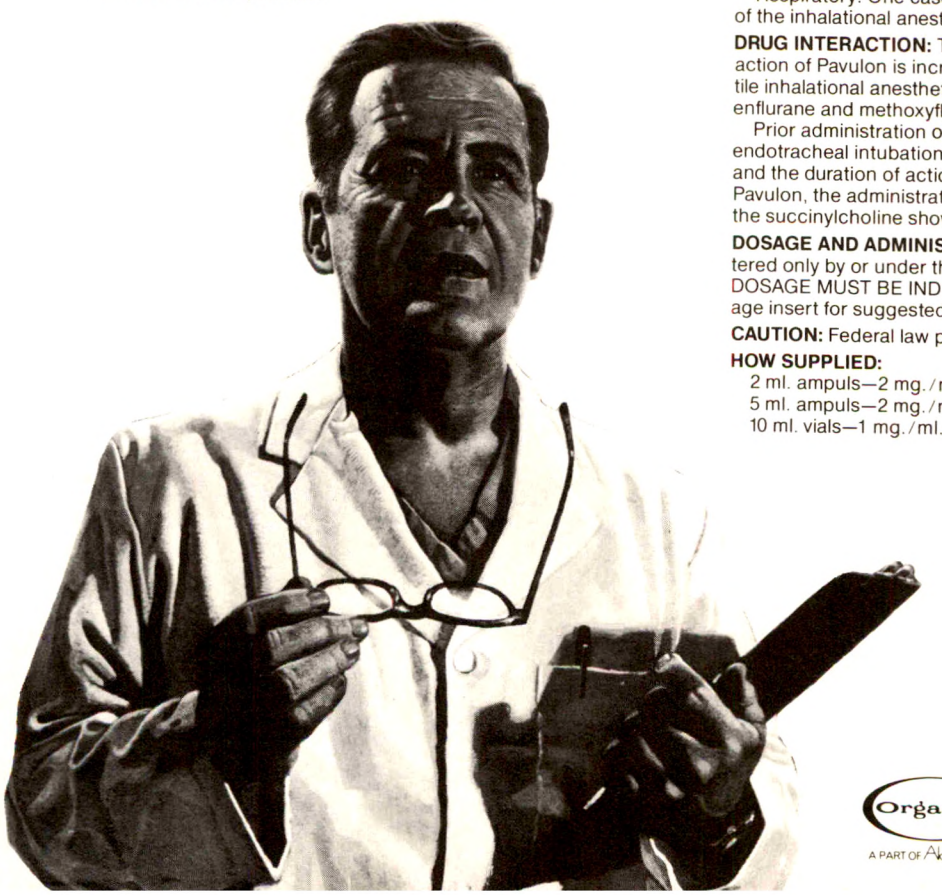
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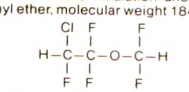
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$T = °C + 273.16$ (Kelvin)

The specific gravity (25°/25°C) is 1.517. The refractive index at 20° is 1.3026-1.3030. The blood/gas coefficient is 1.91 at 37°C and the oil/gas coefficient is 98.5 at 37°C. The M.A.C. (minimum alveolar concentration) in man is 1.68 percent in pure oxygen, 0.57 in 70% nitrous oxide and oxygen, and 1.17 in 30% nitrous oxide and oxygen.

ETHRANE is a clear, colorless, stable liquid whose purity exceeds 99.9 percent (area % by gas chromatography). No chemical stabilizers are added as these have been found, through controlled laboratory tests, to be unnecessary to maintain stability even in the presence of ultraviolet light. ETHRANE is stable to strong base and does not decompose in contact with soda lime and does not attack aluminum, tin, brass, iron or copper. The partition coefficients of ETHRANE at 25°C are 74 in conductive rubber and 120 in polyvinyl chloride.

CLINICAL PHARMACOLOGY

ETHRANE (enflurane) is an inhalation anesthetic. Induction and recovery from anesthesia with ETHRANE are rapid. ETHRANE has a mild, sweet odor. There is mild stimulus to salivation or tracheobronchial secretions when ETHRANE is used alone. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia changes rapidly with ETHRANE. ETHRANE reduces ventilation as depth of anesthesia increases. High pCO_2 levels can be obtained at deeper levels of anesthesia if ventilation is not supported. ETHRANE provokes a sigh response reminiscent of that seen with diethyl ether.

There is a decrease in blood pressure with induction of anesthesia, followed by a return to near normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding increases in hypotension. Heart rate remains relatively constant without significant bradycardia. Electrocardiographic monitoring or recordings indicate that cardiac rhythm remains stable. Elevation of the carbon dioxide level in arterial blood does not alter cardiac rhythm.

Studies in man indicate a considerable margin of safety in the administration of epinephrine containing solutions during ETHRANE anesthesia. ETHRANE anesthesia has been used in excision of pheochromocytoma in man without ventricular arrhythmias. On the basis of studies in patients anesthetized with ETHRANE and injected with epinephrine containing solutions to achieve hemostasis in a highly vascular area (transphenoidal surgery), it is recommended that 2 micrograms per kilogram (2 μg/kg) of epinephrine may be injected subcutaneously over a 10 minute period. This may be repeated up to 3 times per hour.

Example: Up to 10 ml of 1:100,000 epinephrine containing solution (10 μg/ml) may be injected subcutaneously over a 10 minute period in a 50 kilogram patient judged to have ordinary tolerance to epinephrine administration. No more than 30 ml of 1:100,000 epinephrine containing solution (10 μg/ml) should be administered to such a patient per hour. The concomitant administration of lidocaine enhances the safety of the use of epinephrine during ETHRANE anesthesia. This effect of lidocaine is dose related. All customary precautions in the use of vasoconstrictor substances should be observed.

Example Two: Alternatively, up to 20 ml of 1:200,000 epinephrine containing solution (5 μg/ml) may be substituted for 10 ml of 1:100,000 solution in the above example.

Muscle relaxation may be adequate for intra-abdominal operation at normal levels of anesthesia. Muscle relaxants may be used to achieve greater relaxation and all commonly used muscle relaxants are compatible with ETHRANE. The NONDEPOLARIZING MUSCLE RELAXANTS ARE POTENTIATED. In the normal 70 kg adult, 6 to 9 mg of d-tubocurarine or 1 to 1.5 mg of pancuronium will produce a 90 percent or greater depression of twitch height. Neostigmine does not reverse the direct effect of ETHRANE.

Biotransformation of ETHRANE in man results in low levels of serum fluoride ions averaging 15 μM/L. These levels are well below the 50 μM/L threshold level which can produce minimal renal damage in normal subjects; however, it is possible that these levels could result in damage in patients with severely impaired renal function or those undergoing renal transplantation. Depression of lymphocyte transformation does not follow prolonged ETHRANE anesthesia in man in the absence of surgery. Thus ETHRANE does not depress this aspect of the immune response.

INDICATIONS

ETHRANE (enflurane) may be used for induction and maintenance of general anesthesia. Adequate data have not been developed to establish its application in obstetrical anesthesia.

CONTRAINDICATIONS

Seizure disorders (see WARNINGS).

Known sensitivity to ETHRANE (enflurane) or other halogenated anesthetics.

WARNINGS

Increasing depth of anesthesia with ETHRANE (enflurane) may produce a change in the electroencephalogram characterized by high voltage, fast frequency, progressing through spike-dome complexes alternating with periods of electrical silence to frank seizure activity. The latter may or may not be associated with motor movement. Motor activity, when encountered, generally consists of twitching or "jerks" of various muscle groups; it is self-limiting and can be terminated by lowering the anesthetic concentration. This electroencephalographic pattern associated with deep anesthesia is exacerbated by low arterial carbon dioxide tension. A reduction in ventilation and anesthetic concentration usually suffices to eliminate seizure activity. Cerebral blood flow and metabolism studies in normal volunteers immediately following seizure activity show no evidence of cerebral hypoxia. Mental function testing does not reveal any impairment of performance following prolonged ETHRANE anesthesia associated with or not associated with seizure activity.

Since levels of anesthesia may be altered easily and rapidly, only calibrated vaporizers which measure output with reasonable accuracy should be used. Hypotension and respiratory exchange can serve as a guide to anesthesia depth. Deep levels of anesthesia may produce marked hypotension and respiratory depression.

The action of nondepolarizing relaxants is augmented by ETHRANE. Less than the usual amounts of these drugs should be used. If the usual amounts of nondepolarizing relaxants are given, the time for recovery from myoneural blockade will be longer in the presence of ETHRANE than for other commonly used anesthetics.

Usage in Pregnancy: Safety in pregnancy has not been established. Reproduction studies have been performed in rats and rabbits, and there is no evidence of harm to the animal fetus. The relevance of these studies to the human is not known. Since there is no adequate experience in pregnant women who have received the drug, safety in pregnancy has not been established.

PRECAUTIONS

Bromsulfalein (BSP) retention is mildly elevated postoperatively in some cases. This may relate to the effect of surgery since prolonged anesthesia (5 to 7 hours) in human volunteers does not result in BSP elevation. There is some elevation of glucose and white blood count intraoperatively. Glucose elevation should be considered in diabetic patients. ETHRANE (enflurane) should be used with caution in patients who by virtue of medical or drug history could be considered more susceptible to cortical stimulation produced by this drug. As with other general anesthetics and some muscle relaxants, hyperpyrexia has been observed with the use of ETHRANE.

ADVERSE REACTIONS

1. Motor activity examplified by movements of various muscle groups and/or seizures may be encountered with deep levels of ETHRANE (enflurane) anesthesia, or light levels with hypocapnia.
2. Hypotension and respiratory depression have been reported.
3. Arrhythmias, shivering, nausea, and vomiting have been reported.
4. Elevation of the white blood count has been observed.

DOSAGE AND ADMINISTRATION

The concentration of ETHRANE (enflurane) being delivered during anesthesia from a vaporizer should be known. This may be accomplished by using:

a) vaporizers calibrated specifically for ETHRANE.

b) vaporizers from which delivered flows can easily and readily be calculated.

Nothing is present in the agent to alter calibration or affect the operation characteristics of the vaporizer.

Preanesthetic Medication: Preanesthetic medication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by ETHRANE and the heart rate remains constant; the use of anticholinergic drugs is a matter of choice.

Induction: Induction may be achieved using ETHRANE alone with oxygen or in combination with oxygen-nitrous oxide mixtures. Under these conditions some excitement may be encountered. If excitement is to be avoided, a hypnotic dose of a short-acting barbiturate should be used to induce unconsciousness, followed by the ETHRANE mixture. In general, inspired concentrations of 2.0-4.5% ETHRANE produce surgical anesthesia in 7-10 minutes.

Maintenance: Surgical levels of anesthesia may be maintained with 0.5-3% ETHRANE. Maintenance concentrations should not exceed 3%. If added relaxation is required, supplemental doses of muscle relaxants may be used. Ventilation to maintain the tension of carbon dioxide in arterial blood in the 35-45 mm Hg range is preferred. Hyperventilation should be avoided in order to minimize possible CNS excitation.

The level of blood pressure during maintenance is an inverse function of ETHRANE concentration in the absence of other complication problems. Excessive decreases (unless related to hypovolemia) may be due to depth of anesthesia and in such instances should be corrected by lightening the level of anesthesia.

Overdosage: In the event of overdosage, or what may appear to be overdosage, the following action should be taken.

Stop drug administration; establish a clear airway and initiate assisted or controlled ventilation with pure oxygen.

PACKAGING

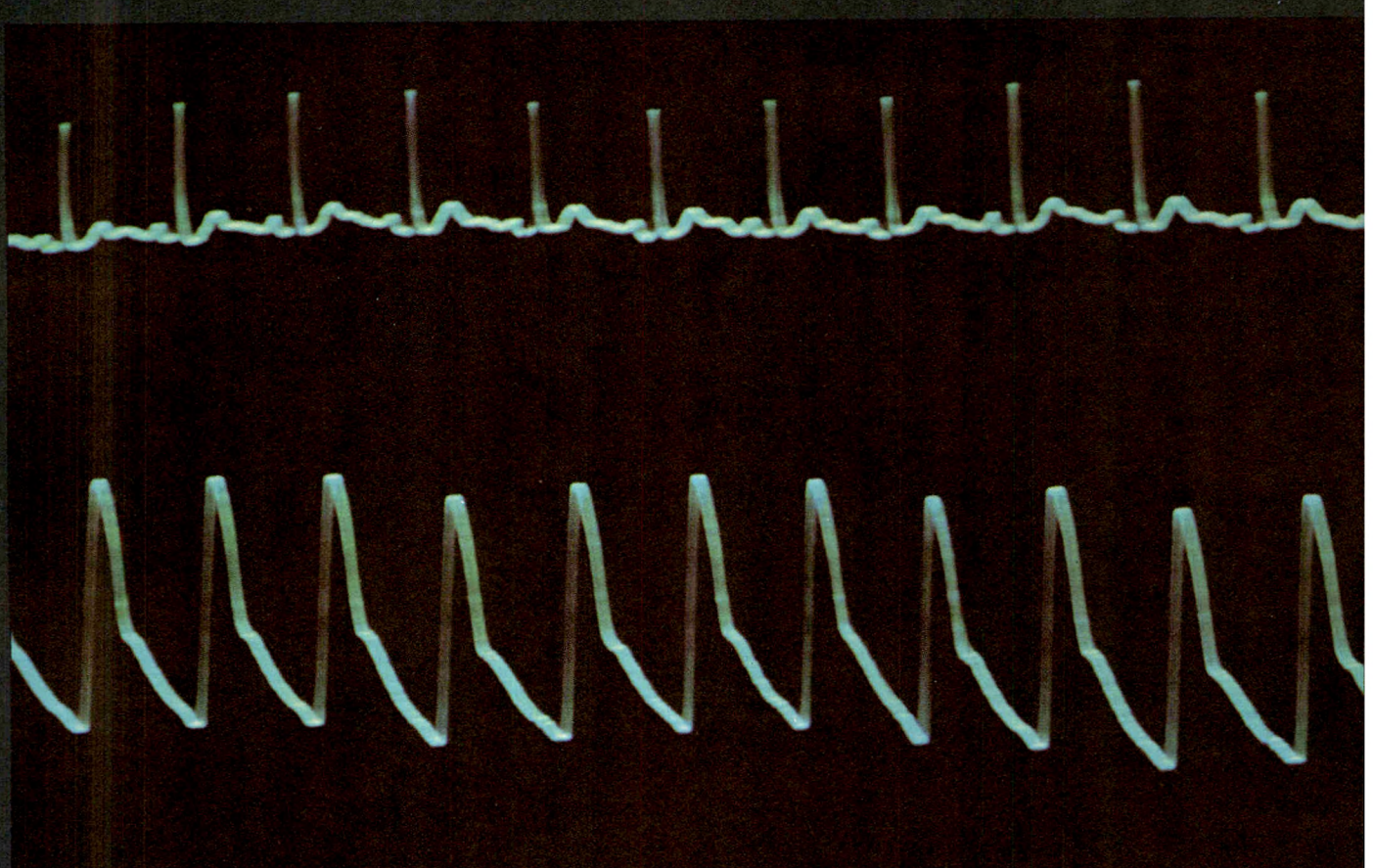
ETHRANE (enflurane) is packaged in 125 and 250 ml amber colored bottles.

Ohio Medical Anesthetics

A Division of Airco, Inc.
3030 Airco Drive, P.O. Box 7550, Madison, Wisconsin 53707
Cable Address: OHIOMED • International Telex: 910-286-2712

Announcing a new anesthetic concept

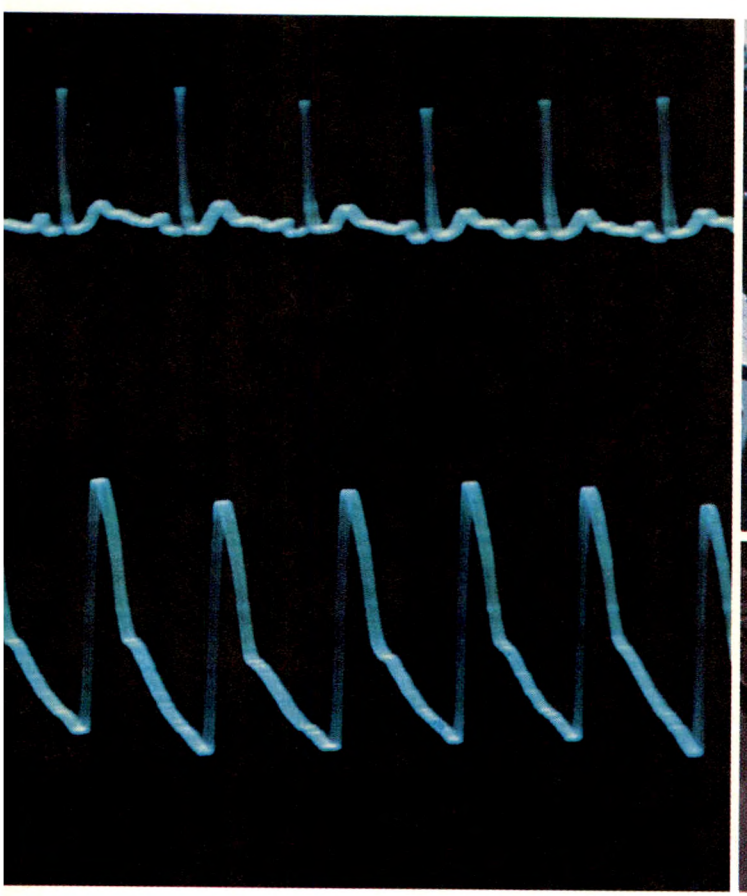
that provides maximum protection prior to maximum stress

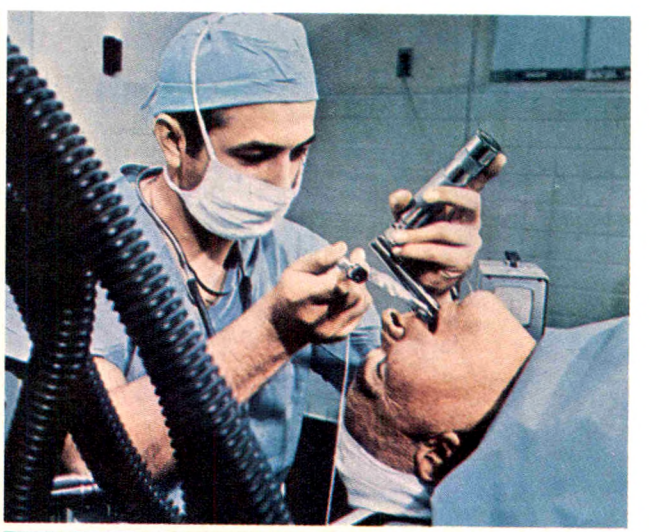


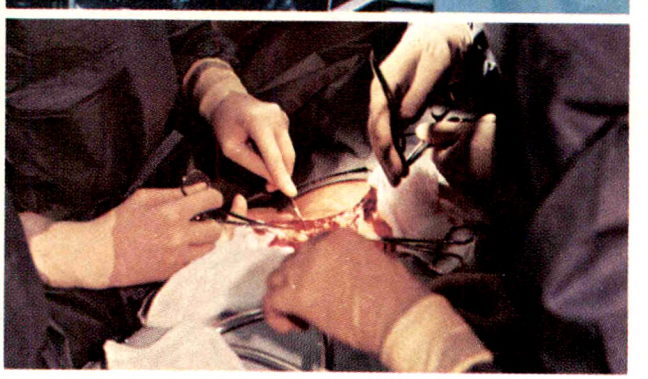
JANSSEN
PHARMACEUTICA

Introducing a new anesthetic technique:

This new technique—pre-intubation analgesic loading—involves administering enough SUBLIMAZE® (fentanyl) prior to intubation to last generally the length of the procedure. Pre-intubation upfront loading employs the pharmacokinetic properties of SUBLIMAZE® (fentanyl) to best advantage compared with p.r.n. use or administration of the drug incrementally throughout the procedure.







For further information and general guidelines on pre-intubation analgesic loading with SUBLIMAZE® (fentanyl), please contact your Janssen representative or write Janssen Pharmaceutica.

JANSSEN PHARMACEUTICA

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Pre-intubation analgesic loading with

Sublimaze®
(fentanyl) Injection C-II

1. Provides maximum protection just prior to anesthetic and surgical stress

Upfront loading immediately before intubation puts the maximum amount of SUBLIMAZE® (fentanyl) on board just prior to laryngoscopy, intubation and incision, the stimuli responsible for maximum stress. (SUBLIMAZE helps attenuate rises in blood pressure and pulse rate.)

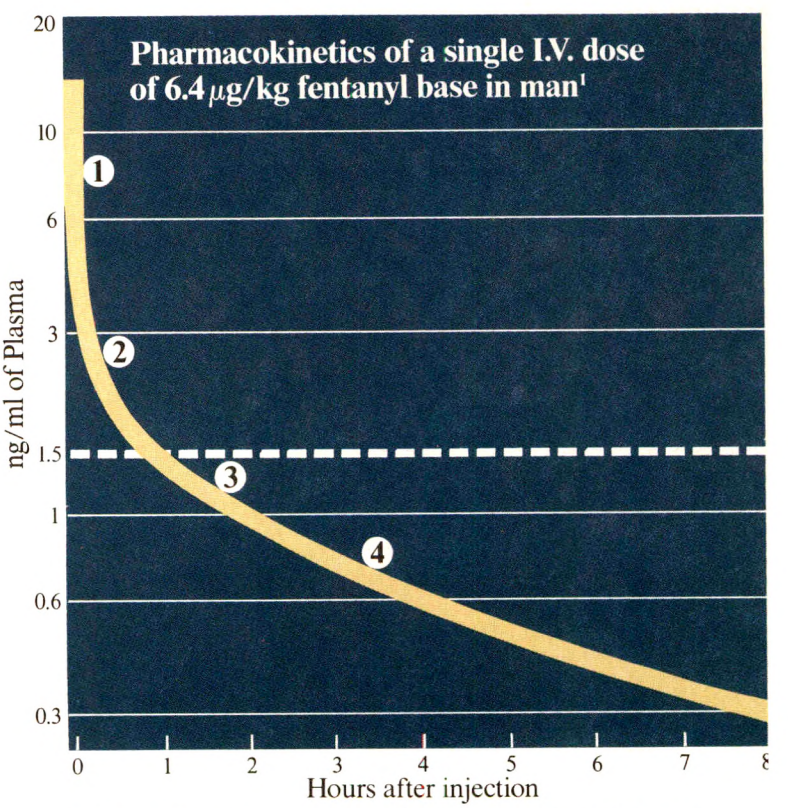
2. Eliminates "chasing the patient"

This new technique helps prevent sympathetic breakthrough and all the problems that stem from "chasing the patient."

3. Permits most patients to breathe spontaneously at completion of surgery*

4. Reduces need for postoperative narcotics

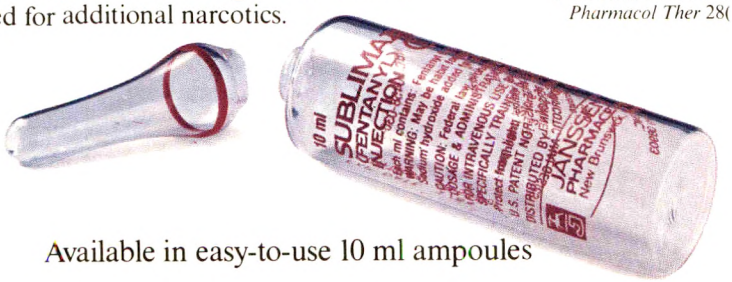
Postoperatively, residual plasma and tissue levels provide sufficient analgesia to minimize the need for additional narcotics.



Slightly depressed spontaneous respiration below 1.5 ng/ml; normal respiration below 0.7ng/ml.[1]

***Note:** Respiratory depression may last longer than analgesic action and this risk increases with increasing doses.

1. McClain DA and Hug CC, Jr.: Intravenous fentanyl kinetics. *Clin Pharmacol Ther* 28(1): 106-114, 1980.



Available in easy-to-use 10 ml ampoules

Please see brief summary of Prescribing Information on next page

Sublimaze®
(fentanyl) Injection

Protect from light. Store at room temperature.

Before prescribing, please consult complete prescribing information, of which the following is a brief summary.

FOR INTRAVENOUS OR INTRAMUSCULAR USE ONLY

DESCRIPTION

Each ml. contains:
Fentanyl ..... 50 mcg. (0.05 mg.) as the citrate
Warning: May be habit forming.
Sodium hydroxide for adjustment of pH to 4.0-7.5.

CONTRAINDICATIONS

SUBLIMAZE (fentanyl) is contraindicated in patients with known intolerance to the drug.

WARNINGS

AS WITH OTHER CNS DEPRESSANTS, PATIENTS WHO HAVE RECEIVED *SUBLIMAZE* (fentanyl) SHOULD HAVE APPROPRIATE SURVEILLANCE.

RESUSCITATION EQUIPMENT AND A NARCOTIC ANTAGONIST SHOULD BE READILY AVAILABLE TO MANAGE APNEA.

See also discussion of narcotic antagonists in Precautions and Overdosage.

If SUBLIMAZE (fentanyl) is administered with a tranquilizer such as *INAPSINE* (droperidol), the user should familiarize himself with the special properties of each drug, particularly the widely differing duration of action. In addition, when such a combination is used, *fluids and other countermeasures to manage hypotension should be available.*

As with other potent narcotics, the respiratory depressant effect of SUBLIMAZE (fentanyl) may persist longer than the measured analgesic effect. The total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, should be used in reduced doses initially, as low as 1/4 to 1/3 those usually recommended. SUBLIMAZE (fentanyl) may cause muscle rigidity, particularly involving the muscles of respiration. The effect is related to the speed of injection and its incidence can be reduced by the use of slow intravenous injection. Once the effect occurs, it is managed by the use of assisted or controlled respiration and, if necessary, by a neuromuscular blocking agent compatible with the patient's condition. Where moderate or high doses are used (above 10 mcg./kg.), there must be adequate facilities for postoperative observation, and ventilation if necessary, of patients who have received SUBLIMAZE (fentanyl). It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

Drug Dependence—SUBLIMAZE (fentanyl) can produce drug dependence of the morphine type and, therefore, has the potential for being abused.

Severe and unpredictable potentiation by MAO inhibitors has been reported with narcotic analgesics. Since the safety of fentanyl in this regard has not been established, the use of SUBLIMAZE (fentanyl) in patients who have received MAO inhibitors within 14 days is not recommended.

Head Injuries and Increased Intracranial Pressure—SUBLIMAZE (fentanyl) should be used with caution in patients who may be particularly susceptible to respiratory depression, such as comatose patients who may have a head injury or brain tumor. In addition SUBLIMAZE (fentanyl) may obscure the clinical course of patients with head injury.

Usage in Children—The safety of SUBLIMAZE (fentanyl) in children younger than two years of age has not been established.

Usage in Pregnancy—The safe use of SUBLIMAZE (fentanyl) has not been established with respect to possible adverse effects upon fetal development. Therefore, it should be used in women of childbearing potential only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. There are insufficient data regarding placental transfer and fetal effects; therefore, safety for the infant in obstetrics has not been established.

PRECAUTIONS

The initial dose of SUBLIMAZE (fentanyl) should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining incremental doses. Nitrous oxide has been reported to produce cardiovascular depression when given with higher doses of fentanyl.

Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can alter respiration by blocking intercostal nerves. Through other mechanisms SUBLIMAZE (fentanyl) can also alter respiration. Therefore, when SUBLIMAZE (fentanyl) is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for these forms of anesthesia.

When used with a tranquilizer such as *INAPSINE* (droperidol), blood pressure may be altered and hypotension can occur.

Vital signs should be monitored routinely.

SUBLIMAZE (fentanyl) should be used with caution in patients with chronic obstructive pulmonary disease, patients with decreased respiratory reserve, and others with potentially compromised respiration. In such patients, narcotics may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Respiratory depression caused by narcotic analgesics can be reversed by narcotic antagonists. Appropriate surveillance should be maintained because the duration of respiratory depression of doses of fentanyl employed during anesthesia may be longer than the duration of the narcotic antagonist action. Consult individual prescribing information (levallorphan, nalorphine and naloxone) before employing narcotic antagonists.

When a tranquilizer such as *INAPSINE* (droperidol) is used with SUBLIMAZE (fentanyl) pulmonary arterial pressure may be decreased. This fact should be considered by those who conduct diagnostic and surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient. When high dose or anesthetic dosages of SUBLIMAZE (fentanyl) are employed, even relatively small dosages of diazepam may cause cardiovascular depression.

Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, and general anesthetics) will have additive or potentiating effects with SUBLIMAZE (fentanyl). When patients have received such drugs, the dose of SUBLIMAZE (fentanyl) required will be less than usual. Likewise, following the administration of SUBLIMAZE (fentanyl), the dose of other CNS depressant drugs should be reduced.

SUBLIMAZE (fentanyl) should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.

SUBLIMAZE (fentanyl) may produce bradycardia, which may be treated with atropine; however, SUBLIMAZE (fentanyl) should be used with caution in patients with cardiac bradyarrhythmias.

When SUBLIMAZE (fentanyl) is used with a tranquilizer such as *INAPSINE* (droperidol) hypotension can occur. If this occurs, the possibility of hypovolemia should also be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should be considered when operative conditions permit. Care should be exercised in moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do not correct hypotension, the administration of pressor agents other than epinephrine should be considered. Because of the alpha-adrenergic blocking action of *INAPSINE* (droperidol), epinephrine may paradoxically decrease the blood pressure in patients treated with *INAPSINE* (droperidol).

When *INAPSINE* (droperidol) is used with SUBLIMAZE (fentanyl) and the EEG is used for postoperative monitoring, it may be found that the EEG pattern returns to normal slowly.

ADVERSE REACTIONS

As with other narcotic analgesics, the most common serious adverse reactions reported to occur with SUBLIMAZE (fentanyl) are respiratory depression, apnea, muscular rigidity, and bradycardia; if these remain untreated, respiratory arrest, circulatory depression or cardiac arrest could occur. Other adverse reactions that have been reported are hypotension, dizziness, blurred vision, nausea, emesis, laryngospasm, and diaphoresis.

It has been reported that secondary rebound respiratory depression may occasionally occur postoperatively. Patients should be monitored for this possibility and appropriate countermeasures taken as necessary.

When a tranquilizer such as *INAPSINE* (droperidol) is used with SUBLIMAZE (fentanyl), the following adverse reactions can occur: chills and/or shivering, restlessness, and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression); extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed up to 24 hours postoperatively. When they occur, extrapyramidal symptoms can usually be controlled with anti-parkinson agents. Postoperative drowsiness is also frequently reported following the use of *INAPSINE* (droperidol).

Elevated blood pressure, with and without pre-existing hypertension, has been reported following administration of SUBLIMAZE (fentanyl) combined with *INAPSINE* (droperidol). This might be due to unexplained alterations in sympathetic activity following large doses; however, it is also frequently attributed to anesthetic and surgical stimulation during light anesthesia.

DOSAGE AND ADMINISTRATION

50 mcg. = .05 mg. = 1 ml.

Dosage should be individualized. Some of the factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and the surgical procedure involved.

Vital signs should be monitored routinely.

I. *Premedication*—Premedication (to be appropriately modified in the elderly, debilitated, and those who have received other depressant drugs)—50 to 100 mcg. (0.05 to 0.1 mg.)(1 to 2 ml.) may be administered *intramuscularly* 30 to 60 minutes prior to surgery.

II. *Adjunct to General Anesthesia*—See Dosage Range Chart

III. *Adjunct to Regional Anesthesia*—50 to 100 mcg. (0.05 to 0.1 mg.)(1 to 2 ml.) may be administered intramuscularly or slowly intravenously, over one to two minutes, when additional analgesia is required.

IV. *Postoperatively (recovery room)*—50 to 100 mcg. (0.05 to 0.1 mg.)(1 to 2 ml.) may be administered intramuscularly for the control of pain, tachypnea and emergence delirium. The dose may be repeated in one to two hours as needed.

Usual Children's Dosage: For induction and maintenance in children 2 to 12 years of age, a reduced dose as low as 20 to 30 mcg. (0.02 to 0.03 mg.)(0.4 to 0.6 ml.) per 20 to 25 pounds is recommended.

DOSAGE RANGE CHART

TOTAL DOSAGE

Low dose—2 mcg./kg. (.002 mg./kg.) (.04 ml./kg.) SUBLIMAZE® injection. Fentanyl in small doses is most useful for minor, but painful, surgical procedures. In addition to the analgesia during surgery, fentanyl may also provide some pain relief in the immediate postoperative period. *Maintenance:* Additional dosages of SUBLIMAZE® injection are infrequently needed in these minor procedures.

Moderate dose—2-20 mcg./kg. (.002-.02 mg./kg.)(.04-0.4 ml./kg.) SUBLIMAZE® injection. Where surgery becomes more major, a larger dose is required. With this dose, in addition to adequate analgesia, one would expect to see some abolition of the stress response. However, respiratory depression will be such that artificial ventilation during anesthesia is necessary, and careful observation of ventilation postoperatively is essential. *Maintenance:* 25 to 100 mcg. (0.025 to 0.1 mg.)(0.5 to 2.0 ml.) may be administered intravenously or intramuscularly when movement and/or changes in vital signs indicate surgical stress or lightening of analgesia.

High dose—20-50 mcg./kg. (.02-.05 mg./kg.)(0.4-1 ml./kg.) SUBLIMAZE® injection. During open heart surgery and certain more complicated neurosurgical and orthopedic procedures where surgery is more prolonged, and in the opinion of the anesthesiologist, the stress response to surgery would be detrimental to the well being of the patient, dosages of 20-50 mcg./kg. (.02-.05 mg.)(0.4-1 ml.) of SUBLIMAZE® injection with nitrous oxide oxygen have been shown to attenuate the stress response as defined by increased levels of circulating growth hormone, catecholamine, ADH, and prolactin.

When dosages in this range have been used during surgery, postoperative ventilation and observation are essential due to extended postoperative respiratory depression.

The main objective of this technique would be to produce "stress free" anesthesia. *Maintenance:* Maintenance dosage (ranging from 25 mcg. (.025 mg.)(0.5 ml.) to one half the initial loading dose) will be dictated by the changes in vital signs which indicate stress and lightening of analgesia. However, the additional dosage selected must be individualized especially if the anticipated remaining operative time is short.

As a General Anesthetic

When attenuation of the responses to surgical stress is especially important, doses of 50 to 100 mcg./kg. (.05 to 0.1 mg./kg.)(1 to 2 ml./kg.) may be administered with oxygen and a muscle relaxant. This technique has been reported to provide anesthesia without the use of additional anesthetic agents. In certain cases, doses up to 150 mcg./kg. (.15 mg./kg.)(3 ml./kg.) may be necessary to produce this anesthetic effect. It has been used for open heart surgery and certain other major surgical procedures in patients for whom protection of the myocardium from excess oxygen demand is particularly indicated, and for certain complicated neurological and orthopedic procedures.

As noted above, it is essential that qualified personnel and adequate facilities be available for the management of respiratory depression.

See Warnings and Precautions for use of SUBLIMAZE (fentanyl) with other CNS depressants, and in patients with altered response.

OVERDOSAGE

Manifestations: The manifestations of SUBLIMAZE (fentanyl) overdosage are an extension of its pharmacologic actions.

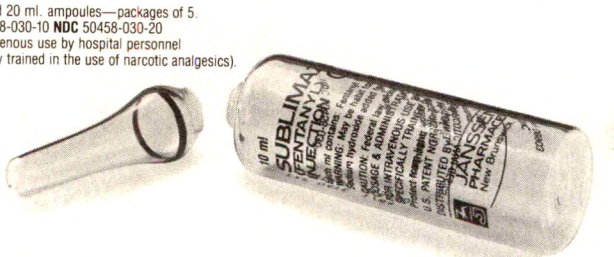
Treatment: In the presence of hypoventilation or apnea, oxygen should be administered and respiration should be assisted or controlled as indicated. A patent airway must be maintained; and oropharyngeal airway or endotracheal tube might be indicated. If depressed respiration is associated with muscular rigidity, an intravenous neuromuscular blocking agent might be required to facilitate assisted or controlled respiration. The patient should be carefully observed for 24 hours; body warmth and adequate fluid intake should be maintained. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. A specific narcotic antagonist such as nalorphine, levallorphan, or naloxone should be available for use as indicated to manage respiratory depression. This does not preclude the use of more immediate countermeasures. The duration of respiratory depression following overdosage of fentanyl may be longer than the duration of narcotic antagonist action. Consult the package insert of the individual narcotic antagonists for details about use.

HOW SUPPLIED

2 ml. and 5 ml. ampoules—packages of 10.
NDC 50458-030-02 **NDC** 50458-030-05

10 ml. and 20 ml. ampoules—packages of 5.
NDC 50458-030-10 **NDC** 50458-030-20
(For intravenous use by hospital personnel specifically trained in the use of narcotic analgesics).

March, 1980. Revised June, 1980. January 1981
U.S. Patent No. 3, 164 600



world leader in anesthesia research

JANSSEN PHARMACEUTICA

Janssen Pharmaceutica Inc., 501 George St., New Brunswick, N.J. 08903

JPI-255



The new BEAR® 2 Ventilator has all the reliability of the old... and a lot more capability. When you see it, you'll know we've been listening.

Think about it! We added the features that you've been asking for. An extended operating range with higher pressure and PEEP levels, and a lower flow rate capability. All this means you can ventilate more types of patients and more lung conditions than ever... with our BEAR® 2 Ventilator.

The BEAR® 2 Ventilator offers a wider array of alarms and alerts ...such as adjustable apnea and over-temperature... and still there's much more.

Together these systems increase versatility, provide more information and give you a better cost/benefit ratio. Ask

The New Old Reliable.



The BEAR® 2 Ventilator.

You'll still find the features that made the BEAR® 1 Ventilator number one in the market... but now, the BEAR® 2 Ventilator... the same old reliability... and more new capability. All this and more.

You can't afford to be without it.

For more information or a demonstration, contact us directly at 1-800-854-5245 or circle the reader's service card for a demo or for literature.

Bear

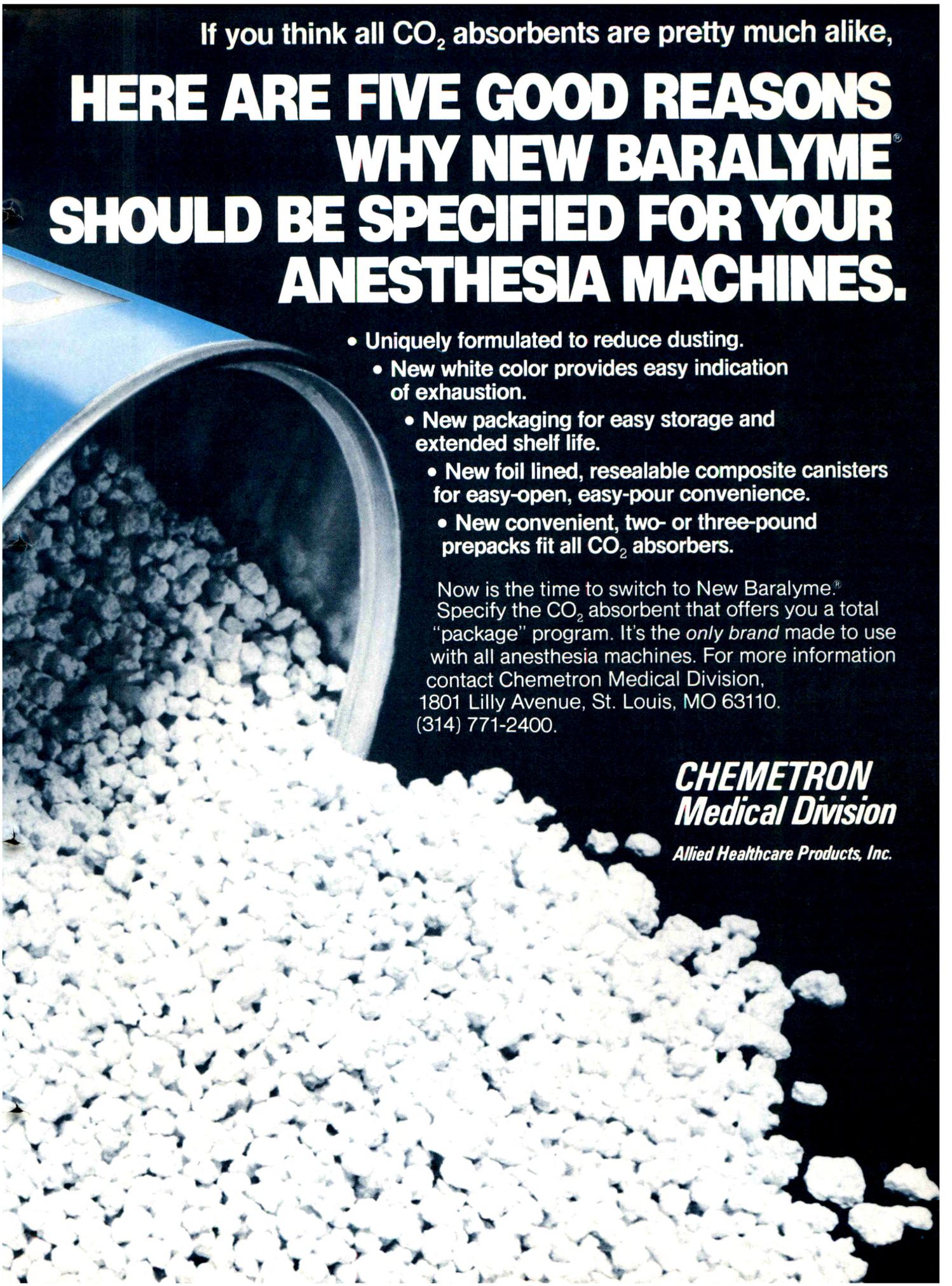
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Bear Medical Systems, Inc.
formerly Bourns Medical Systems, Inc.
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Riverside, California 92503



THE TOTAL PACKAGE

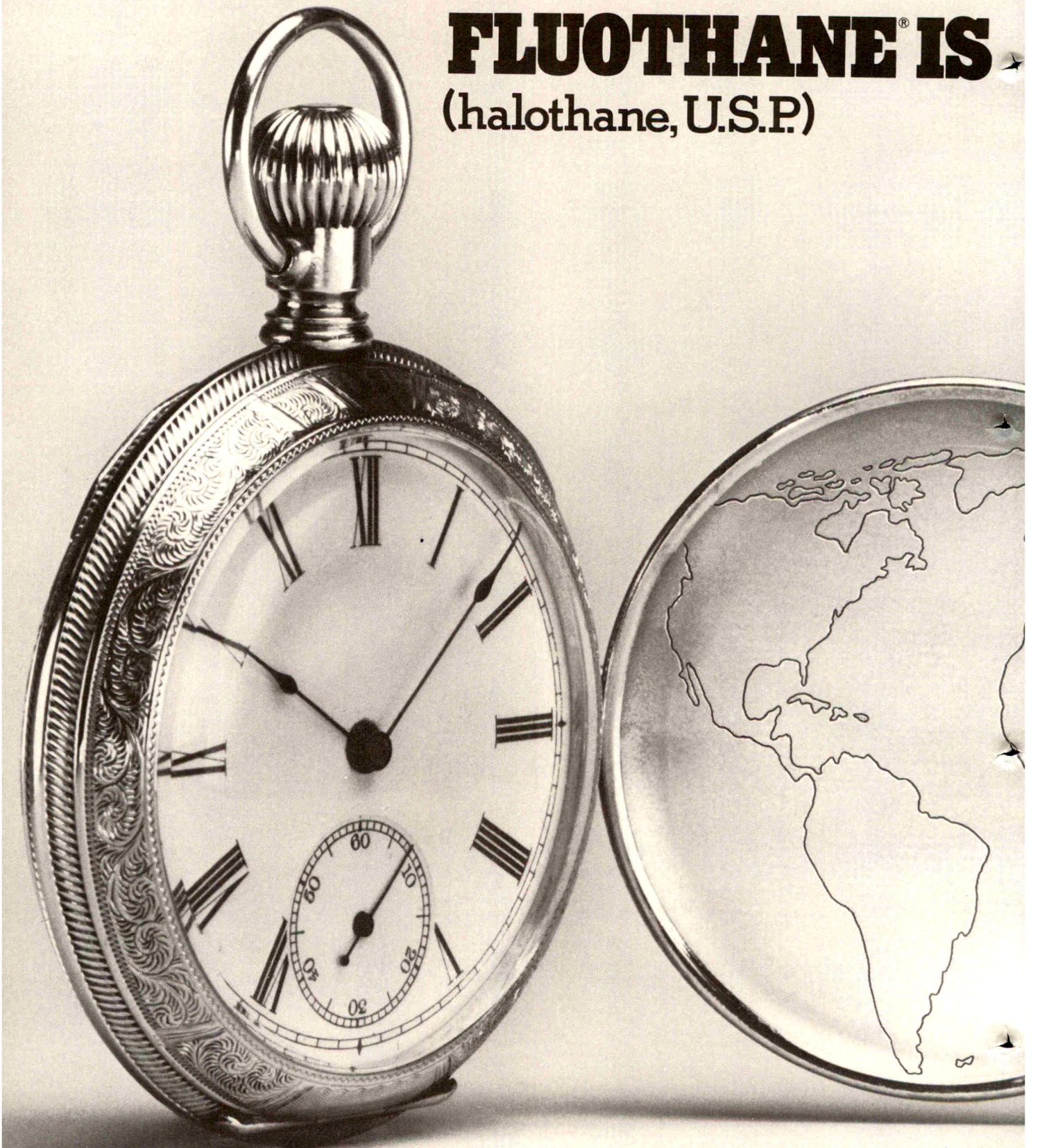
New Baralyme® CO_2 absorbent offers you a choice of convenient dispensers: a forty-pound bulk plastic barrel; three-pound, foil lined resealable canister and a two- or three-pound, ready-to-use prepack. The new three-pound disposable prepack fits most absorbers on the market today. Best of all, no matter which container fits your needs, you'll be getting the only CO_2 absorbent specially formulated to reduce dusting... and the only brand packaged to fit all CO_2 absorbers.


If you think all CO_2 absorbents are pretty much alike,
HERE ARE FIVE GOOD REASONS WHY NEW BARALYME® SHOULD BE SPECIFIED FOR YOUR ANESTHESIA MACHINES.
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Now is the time to switch to New Baralyme.® Specify the CO_2 absorbent that offers you a total "package" program. It's the *only brand* made to use with all anesthesia machines. For more information contact Chemetron Medical Division, 1801 Lilly Avenue, St. Louis, MO 63110. (314) 771-2400.
CHEMETRON Medical Division
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EVERY TWO SECONDS

FLUOTHANE® IS

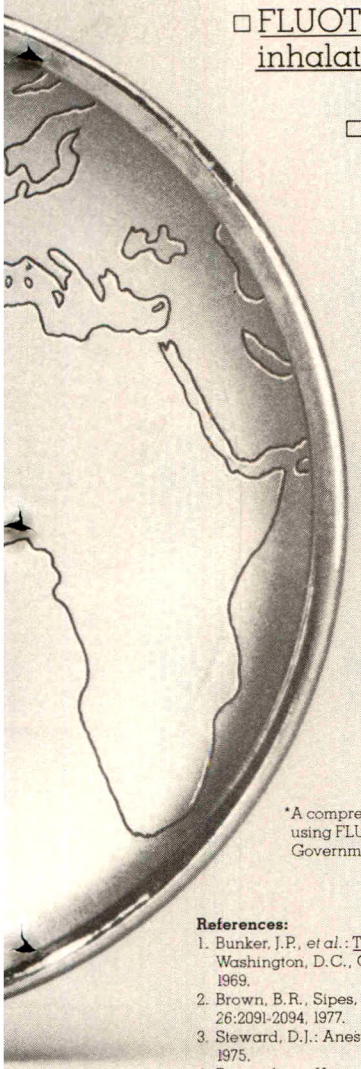
(halothane, U.S.P.)



THE WORLDWIDE CHOICE.

Over 500 million administrations throughout the world. Well over 125 million administrations in the United States alone.

Somewhere in the world—every two seconds—someone makes another decision to use FLUOTHANE® (halothane, U.S.P.). And for good reasons:



- FLUOTHANE has been more widely investigated than any other inhalation anesthetic.
- The FLUOTHANE experience shows association with hepatotoxicity to be extremely rare.[1] According to conclusions drawn from the United States National Halothane Study and other studies,* unexplained jaundice following anesthesia with halothane "...was a rare occurrence (approximately 1:30,000 administrations) and... the overall safety record of the anesthetic was excellent."[2]
- FLUOTHANE "...is nearest to the ideal [inhalation anesthetic] presently available for children of all ages."[3]
- FLUOTHANE has been recommended as the "anesthetic of choice"[4] for asthmatics.
- And, of particular benefit in geriatrics and cardiovascular surgery: Excessive respiratory depression is rarely a problem with FLUOTHANE. Nor does it produce an increase in salivary or bronchial secretions.

*A comprehensive retrospective analysis covering 856,000 general anesthesias—nearly one-third using FLUOTHANE. Bunker, J.P., *et al.*: The National Halothane Study. Washington, D.C., Government Printing Office, 1969.

References:

1. Bunker, J.P., *et al.*: The National Halothane Study. Washington, D.C., Government Printing Office, 1969.
2. Brown, B.R., Sipes, I.G.: Biochem. Pharmacol. 26:2091-2094, 1977.
3. Steward, D.J.: Anesthesiology 43:268-276 (Aug.) 1975.
4. Proceedings, Virginia Society of Anesthesiologists, April 20-22, 1979, Richmond, VA.

See following page for Brief Summary.

Ayerst Laboratories
New York, N.Y. 10017

the most widely used inhalation anesthetic in the world

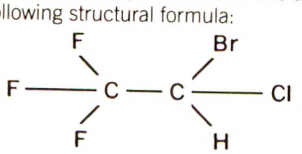
FLUOTHANE®
(halothane, U.S.P.)

for a wide variety of techniques and procedures in patients of all ages



(Complete text of package circular.)

Description. FLUOTHANE, brand of halothane, U.S.P., is an inhalation anesthetic. It is 2-bromo-2-chloro-1, 1, 1-trifluoroethane and has the following structural formula:



The specific gravity is 1.872-1.877 at 20°C, and the boiling point (range) is 49°C – 51°C at 760 mm Hg. The vapor pressure is 243 mm Hg at 20°C. The blood/gas coefficient is 2.5 at 37°C, and the olive oil/water coefficient is 220 at 37°C. Vapor concentrations within anesthetic range are nonirritating and have a pleasant odor. FLUOTHANE is nonflammable, and its vapors mixed with oxygen in proportions from 0.5 to 50 per cent (v/v) are not explosive.

FLUOTHANE does not decompose in contact with warm soda lime. When moisture is present, the vapor attacks aluminum, brass, and lead, but not copper. Rubber, some plastics, and similar materials are soluble in FLUOTHANE; such materials will deteriorate rapidly in contact with FLUOTHANE vapor or liquid. Stability of FLUOTHANE is maintained by the addition of 0.01 per cent thymol (w/w), up to 0.00025% ammonia (w/w), and storage is in amber colored bottles.

FLUOTHANE should not be kept indefinitely in vaporizer bottles not specifically designed for its use. Thymol does not volatilize along with FLUOTHANE, and therefore accumulates in the vaporizer, and may, in time, impart a yellow color to the remaining liquid or to wicks in vaporizers. The development of such discoloration may be used as an indicator that the vaporizer should be drained and cleaned, and the discolored FLUOTHANE (halothane, U.S.P.) discarded. Accumulation of thymol may be removed by washing with diethyl ether. After cleaning a wick or vaporizer, make certain all diethyl ether has been removed before reusing the equipment to avoid introducing ether into the system.

Actions. FLUOTHANE is an inhalation anesthetic. Induction and recovery are rapid and depth of anesthesia can be rapidly altered. FLUOTHANE progressively depresses respiration. There may be tachypnea with reduced tidal volume and alveolar ventilation. FLUOTHANE is not an irritant to the respiratory tract, and no increase in salivary or bronchial secretions ordinarily occurs. Pharyngeal and laryngeal reflexes are rapidly obtunded. It causes bronchodilation. Hypoxia, acidosis, or apnea may develop during deep anesthesia.

FLUOTHANE reduces the blood pressure, and frequently decreases the pulse rate. The greater the concentration of the drug, the more evident these changes become. Atropine may reverse the bradycardia. FLUOTHANE does not cause the release of catecholamines from adrenergic stores. FLUOTHANE also causes dilation of the vessels of the skin and skeletal muscles.

Cardiac arrhythmias may occur during FLUOTHANE anesthesia. These include nodal rhythm, AV dissociation, ventricular extrasystoles and asystole. FLUOTHANE sensitizes the myocardial conduction system to the action of epinephrine and norepinephrine, and the combination may cause serious cardiac arrhythmias. FLUOTHANE increases cerebral spinal fluid pressure. FLUOTHANE produces moderate muscular relaxation. Muscle relaxants are used as adjuncts in order to maintain lighter levels of anesthesia. FLUOTHANE augments the action of nondepolarizing relaxants and ganglionic blocking agents. FLUOTHANE is a potent uterine relaxant.

Indications. FLUOTHANE (halothane, U.S.P.) is indicated for the induction and maintenance of general anesthesia.

Contraindications. FLUOTHANE is not recommended for obstetrical anesthesia except when uterine relaxation is required.

Warnings. When previous exposure to FLUOTHANE was followed by unexplained jaundice, consideration should be given to the use of other agents.

FLUOTHANE should be used in vaporizers that permit a reasonable approximation of output, and preferably of the calibrated type. The vaporizer should be placed out of circuit in closed circuit rebreathing systems; otherwise overdosage is difficult to avoid. The patient should be closely observed for signs of overdosage, *i.e.*, depression of blood pressure, pulse rate, and ventilation, particularly during assisted or controlled ventilation.

Usage in Pregnancy. Safe use of FLUOTHANE has not been established with respect to possible adverse effects upon fetal development. Therefore, FLUOTHANE should not be used in women where pregnancy is possible and particularly during early pregnancy, unless, in the judgment of the physician, the potential benefits outweigh the unknown hazards to the fetus.

Precautions. The uterine relaxation obtained with FLUOTHANE, unless carefully controlled, may fail to respond to ergot derivatives and oxytocic posterior pituitary extract.

FLUOTHANE increases cerebrospinal fluid pressure. Therefore, in patients with markedly raised intracranial pressure, if FLUOTHANE is indicated, administration should be preceded by measures ordinarily used to reduce cerebrospinal fluid pressure. Ventilation should be carefully assessed, and it may be necessary to assist or control ventilation to insure adequate oxygenation and carbon dioxide removal.

Epinephrine or norepinephrine should be employed cautiously, if at all, during FLUOTHANE (halothane, U.S.P.) anesthesia since their simultaneous use may induce ventricular tachycardia or fibrillation.

Nondepolarizing relaxants and ganglionic blocking agents should be administered cautiously, since their actions are augmented by FLUOTHANE.

It has been reported that in genetically susceptible individuals, the use of general anesthetics and the muscle relaxant, succinylcholine, may trigger a syndrome known as malignant hyperthermic crisis. Monitoring temperature during surgery will aid in early recognition of this syndrome. Dantrolene sodium and supportive measures are generally indicated in the management of malignant hyperthermia.

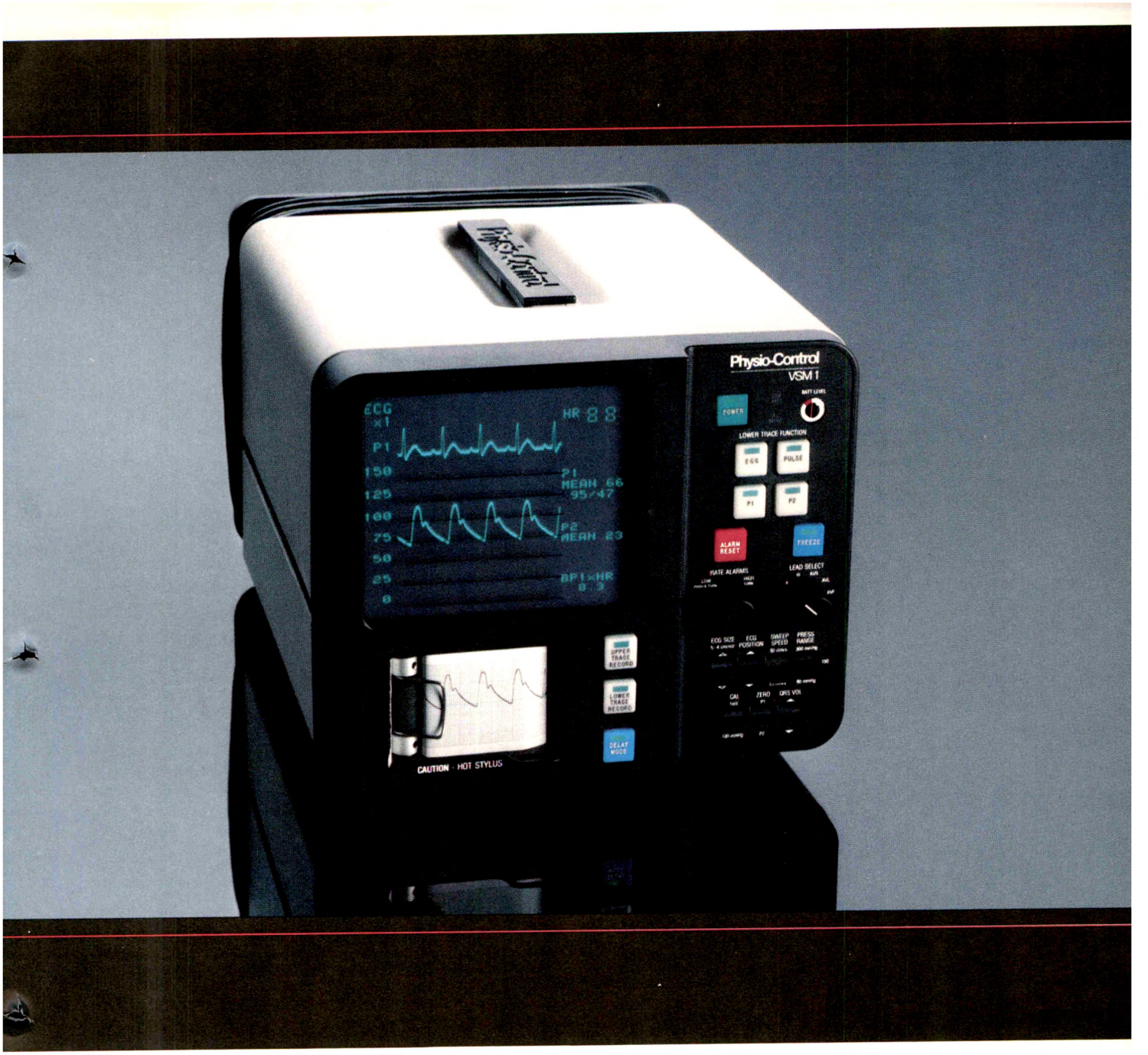
Adverse Reactions. The following adverse reactions have been reported: mild, moderate and severe hepatic dysfunction (including hepatic necrosis), cardiac arrest, hypotension, respiratory arrest, cardiac arrhythmias, hyperpyrexia, shivering, nausea, and emesis.

Dosage and Administration. FLUOTHANE may be administered by the nonrebreathing technic, partial rebreathing, or closed technic. The induction dose varies from patient to patient. The maintenance dose varies from 0.5 per cent to 1.5 per cent.

FLUOTHANE may be administered with either oxygen or a mixture of oxygen and nitrous oxide.

How Supplied. No. 3125—Unit packages of 125 ml and 250 ml of halothane, U.S.P., stabilized with 0.01% thymol (w/w), and up to 0.00025% ammonia (w/w). **7197/R82**

Ayerst Ayerst Laboratories
New York, N.Y. 10017



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Although it has been on the market for little more than one year, VSM™ 1 Vital Signs Monitor has already logged more than one million hours of operation. And during that time, the VSM 1 has established an enviable reputation for accuracy and reliability. The VSM 1. It is compact. It is portable. It is easy to read. It is simple to operate. And as we say, it is supremely accurate and reliable. The VSM 1. Very positive signs.

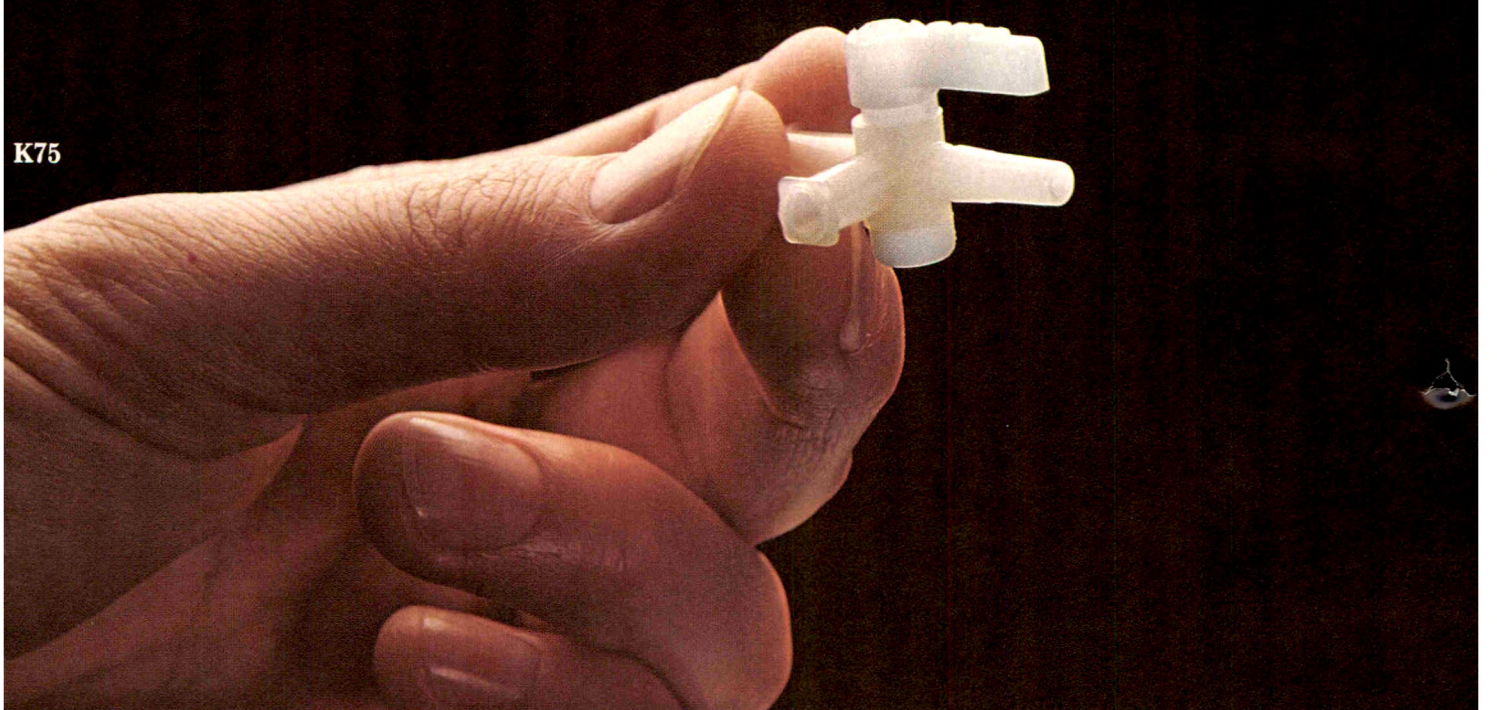
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The VSM 1 Vital Signs Monitor from Physio-Control.

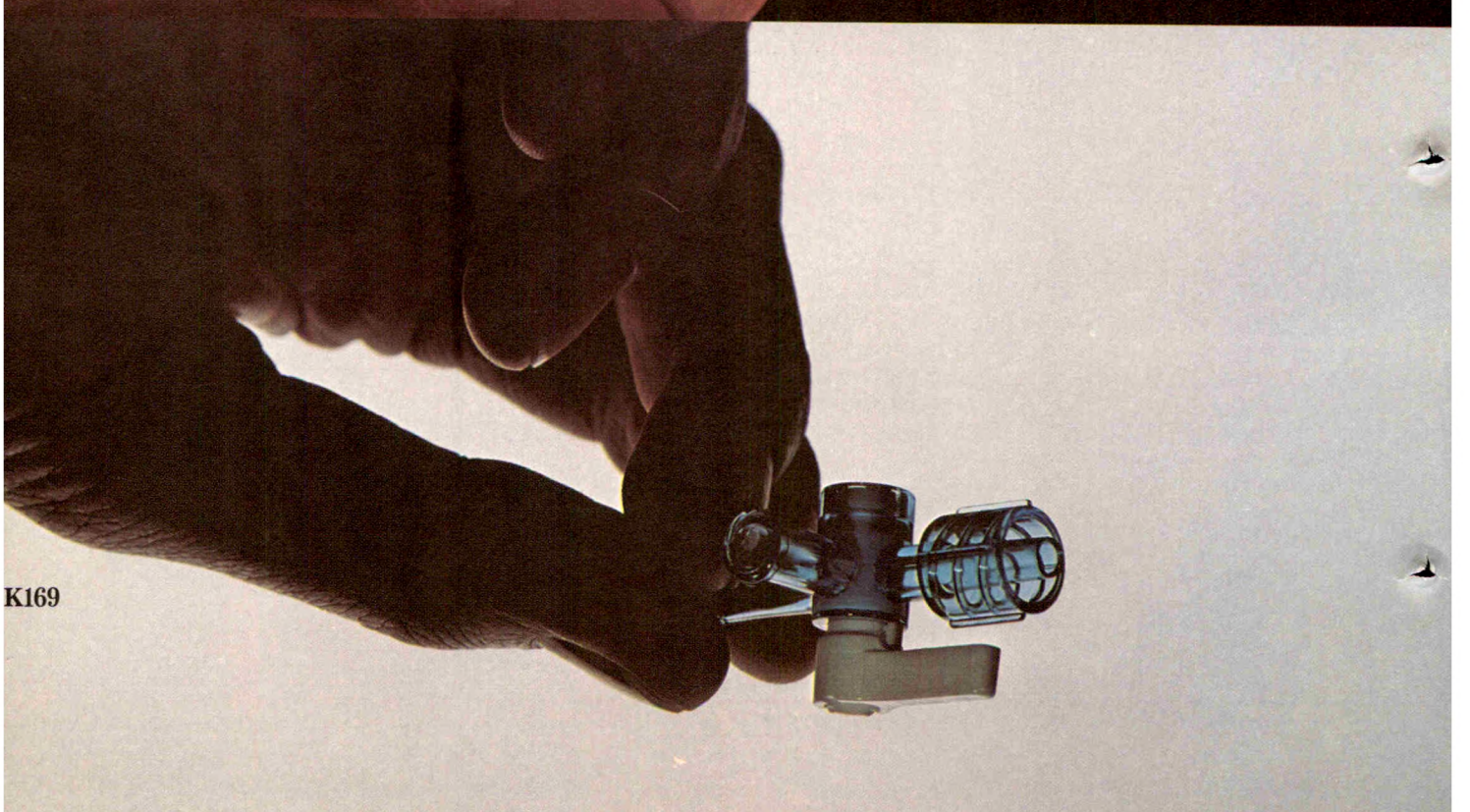
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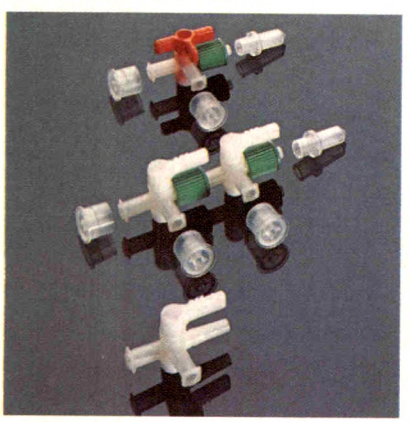
"Get me a K-75..." for example, is heard all day in hospitals all over the country.

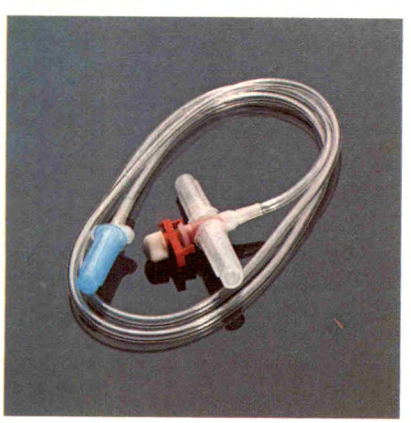
Our K-75 and K-52 Novex® stopcocks are legendary. And they're only part of the most complete and widely used line of general purpose stopcocks available anywhere.

One-way... Three-way... Double and triple tandem three-way...

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All with smooth-turning handles that won't stick or leak in the usual applications.

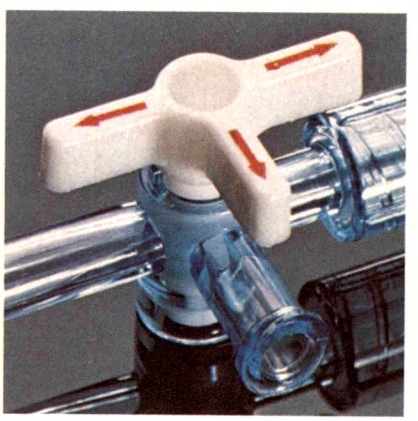
And now, a complete line of K-Series clear stopcocks for invasive monitoring.

Our latest innovation is the K-Series clear stopcocks designed for invasive monitoring.

The transparent light blue body makes air bubbles very easy to see with visual inspection. So there's no need to worry about hidden air bubbles.

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These non-leaking stopcocks feature Luer-lock fittings. They're superb units, just what you need for invasive monitoring.



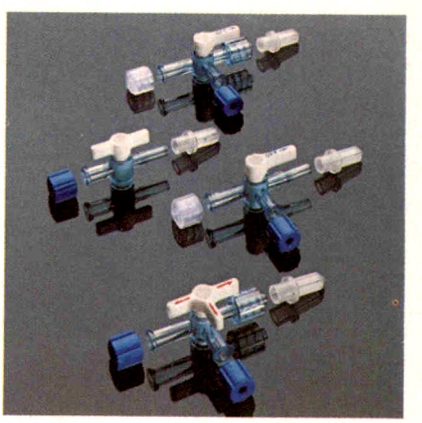
25 million later.

That's how many we've made. That's a lot of experience.

Every one is produced with the strictest quality control standards under stringent biological, chemical and physical testing.

The result, highest quality American Pharmaseal stopcocks.

Our K-Series stopcocks. Now that you know who makes them, we may hear you saying, "Get me the *Pharmaseal*® K-75..."



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STADOL®
(BUTORPHANOL TARTRATE)
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SAFETY IS THE DIFFERENCE

For an uneventful anesthesia course

In preop, you'll appreciate the good sedative effect of Stadol and reduction in patient apprehension.

Intraoperatively, Stadol provides smooth induction and emergence. The return to spontaneous respiration is rapid, so naloxone is rarely required.

In the recovery room, dosage can be repeated or increased, if necessary, to provide full pain relief with little fear of causing respiratory depression greater than that produced by 10 mg morphine.



Rebound respiratory depression, as sometimes seen in recovery after fentanyl, does not occur. Hypotensive effects are limited. Nausea or vomiting is rare.

Stadol is adaptable to a wide range of procedures, is compatible with your routines and is nonscheduled so you can keep it conveniently on your anesthesia cart.

Note: Stadol should not be administered to patients who have significant recent narcotic experience; its narcotic antagonist properties may induce withdrawal reactions unless detoxification is accomplished prior to use.

Stadol® IM IV

(butorphanol tartrate)

for moderate to severe pain…
the hospital-proven analgesic
with the safety difference

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Please see brief summary of prescribing information on adjoining page.

Stadol® IM IV
(butorphanol tartrate)

the effective analgesic with the safety difference

Brief Summary of Prescribing Information
STADOL® (butorphanol tartrate)

For complete information, consult Official Package Circular.

(2) 12/10/79

INDICATIONS AND USAGE—Stadol is recommended for the relief of moderate to severe pain. Stadol can also be used for preoperative or preanesthetic medication, as a supplement to balanced anesthesia, and for the relief of prepartum pain.

CONTRAINDICATIONS—Stadol should not be administered to patients who have been shown to be hypersensitive to it.

WARNINGS—Patients Physically Dependent on Narcotics: Because of its antagonist properties, Stadol is not recommended for patients physically dependent on narcotics. Detoxification in such patients is required prior to use.
Due to the difficulty in assessing addiction in patients who have recently received substantial amounts of narcotic medication, caution should be used in the administration of Stadol. Detoxification of such patients prior to usage should be carefully considered.

Drug Dependence: Special care should be exercised in administering Stadol to emotionally unstable patients and to those with a history of drug misuse. When long-term therapy is contemplated, such patients should be closely supervised. Even though Stadol has a low physical dependence liability, care should be taken that individuals who may be prone to drug abuse are closely supervised. It is important to avoid increases in dose and frequency of injections by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

Head Injury and Increased Intracranial Pressure: Although there is no clinical experience in patients with head injury, it can be assumed that Stadol, like other potent analgesics, elevates cerebrospinal fluid pressure. Therefore the use of Stadol in cases of head injury can produce effects (e.g., miosis) which may obscure the clinical course of patients with head injuries. In such patients Stadol must be used with extreme caution and only if its use is deemed essential.

Cardiovascular Effects: Because Stadol increases the work of the heart, especially the pulmonary circuit, the use of this drug in acute myocardial infarction or in cardiac patients with ventricular dysfunction or coronary insufficiency should be limited to those who are hypersensitive to morphine sulfate or meperidine.

PRECAUTIONS—Certain Respiratory Conditions: Because Stadol causes some respiratory depression, it should be administered only with caution and low dosage to patients with respiratory depression (e.g., from other medication, uremia, or severe infection), severely limited respiratory reserve, bronchial asthma, obstructive respiratory conditions, or cyanosis.

Impaired Renal or Hepatic Function: Although laboratory tests have not indicated that Stadol causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Extensive liver disease may predispose to greater side effects and greater activity from the usual clinical dose, possibly the result of decreased metabolism of the drug by the liver.

Biliary Surgery: Clinical studies have not been done to establish the safety of Stadol administration to patients about to undergo surgery of the biliary tract.

Usage as a Preoperative or Preanesthetic Medication: Slight increases in systolic blood pressure may occur, therefore caution should be employed when Stadol is used in the hypertensive patient.

Usage in Balanced Anesthesia: The use of pancuronium in combination with Stadol may cause an increase in conjunctival changes.

Usage in Pregnancy: The safety of Stadol for use in pregnancy prior to the labor period has not been established; therefore, this drug should be used in pregnant patients only when in the judgment of the physician its use is deemed essential to the welfare of the patient.
Reproduction studies have been performed in rats, mice and rabbits and have revealed no evidence of impaired fertility or harm to the fetus due to Stadol at about 2.5 to 5 times the human dose.

Usage in Labor and Delivery: Safety to the mother and fetus following administration of Stadol during labor has been established. Patients receiving Stadol during labor have experienced no adverse effects other than those observed with commonly used analgesics. Stadol should be used with caution in women delivering premature infants.

Usage in Nursing Mothers: The use of Stadol in lactating mothers who are nursing their infants is not recommended since it is not known whether this drug is excreted in human milk. Stadol has been used safely for labor pain in mothers who subsequently nursed their infants.

Usage in Children: Safety and efficacy in children below age 18 years have not been established.

ADVERSE REACTIONS—The most frequent adverse reactions in 1250 patients treated with Stadol are: sedation (503, 40%), nausea (82, 6%), clammy/sweating (76, 6%).
Less frequent reactions are: headache (35, 3%), vertigo (33, 3%), floating feeling (33, 3%), dizziness (23, 2%), lethargy (19, 2%), confusion (15, 1%), lightheadedness (12, 1%).
Other adverse reactions which may occur (reported incidence of less than 1%) are:
CNS: nervousness, unusual dreams, agitation, euphoria, hallucinations
Autonomic: flushing and warmth, dry mouth, sensitivity to cold
Cardiovascular: palpitation, increase or decrease of blood pressure
Gastrointestinal: vomiting
Respiratory: slowing of respiration, shallow breathing
Dermatological: rash or hives
Eye: diplopia or blurred vision

OVERDOSAGE—Manifestations: Although there have been no experiences of overdosage with Stadol during clinical trials, this may occur due to accidental or intentional misuse as well as therapeutic use. Based on the pharmacology of Stadol, overdosage could produce some degree of respiratory depression and variable cardiovascular and central nervous system effects.

Treatment: The immediate treatment of suspected Stadol overdosage is intravenous naloxone. The respiratory and cardiac status of the patient should be evaluated constantly and appropriate supportive measures instituted, such as oxygen, intravenous fluids, vasopressors and assisted or controlled respiration.

HOW SUPPLIED—Stadol (butorphanol tartrate) Injection for I.M. or I.V. use, is available as follows:

NDC 0015-5644-20—2 mg per ml, 2-ml vial
NDC 0015-5645-20—1 mg per ml, 1-ml vial
NDC 0015-5646-20—2 mg per ml, 1-ml vial
NDC 0015-5646-23—2 mg per ml, 1-ml Disposable Syringe
NDC 0015-5648-20—2 mg per ml, 10-ml multi-dose vial

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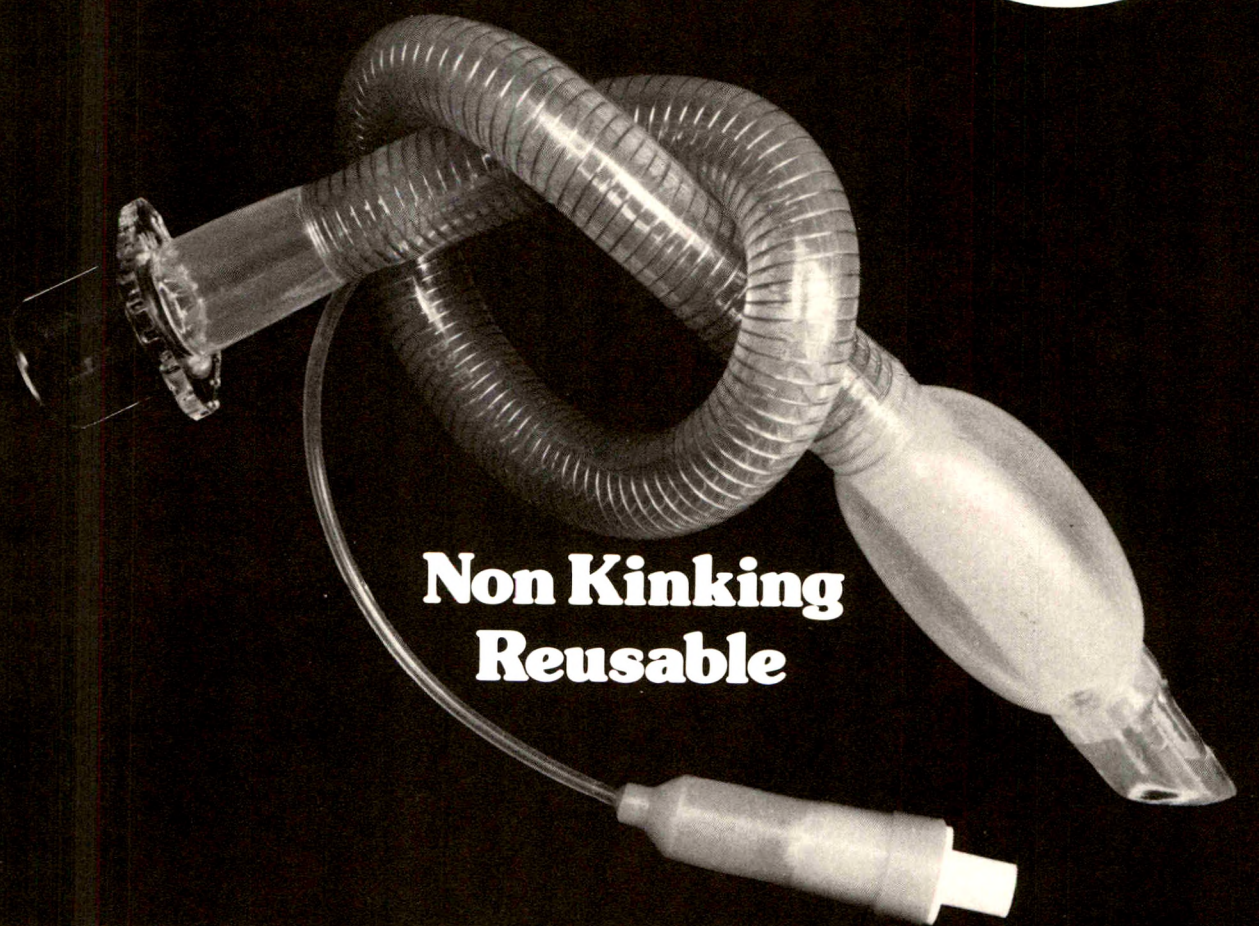
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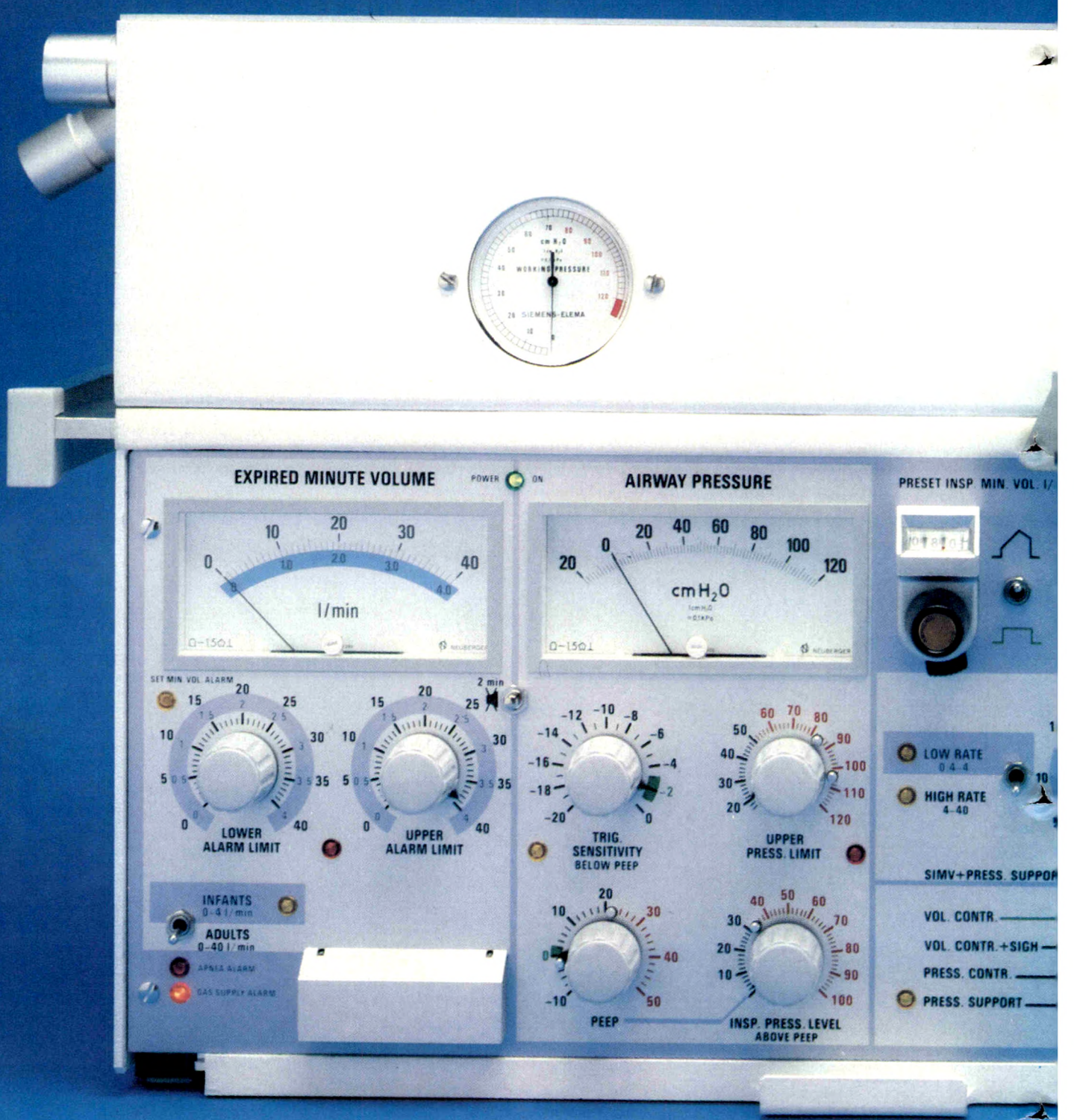
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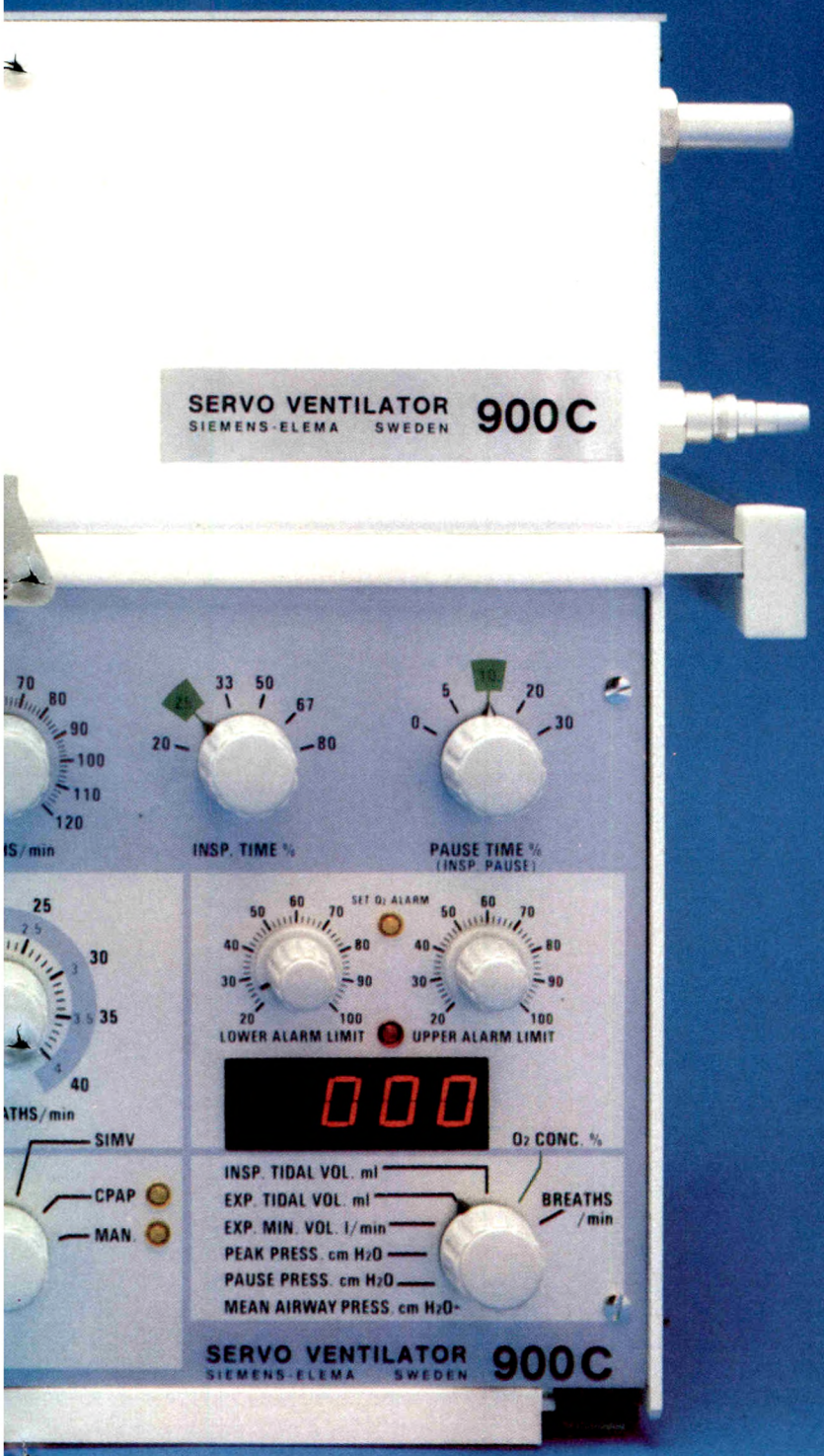
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UPPER PRESS. LIMIT
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0.4-4
HIGH RATE
4-40
INFANTS
0-4 l/min
ADULTS
0-40 l/min
APNEA ALARM
GAS SUPPLY ALARM
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Servo Ventilator 900C is the latest and most advanced of the Servo Ventilators. It is designed for respiratory treatment and monitoring for all age groups in intensive care and anesthesia.

Eight ventilation modes, electronic PEEP and CPAP, digital display of vital patient parameters, expandable scales for adults and infants, stepless SIMV, instant gas change. All parameters are easily interfaced for recording or data storage.

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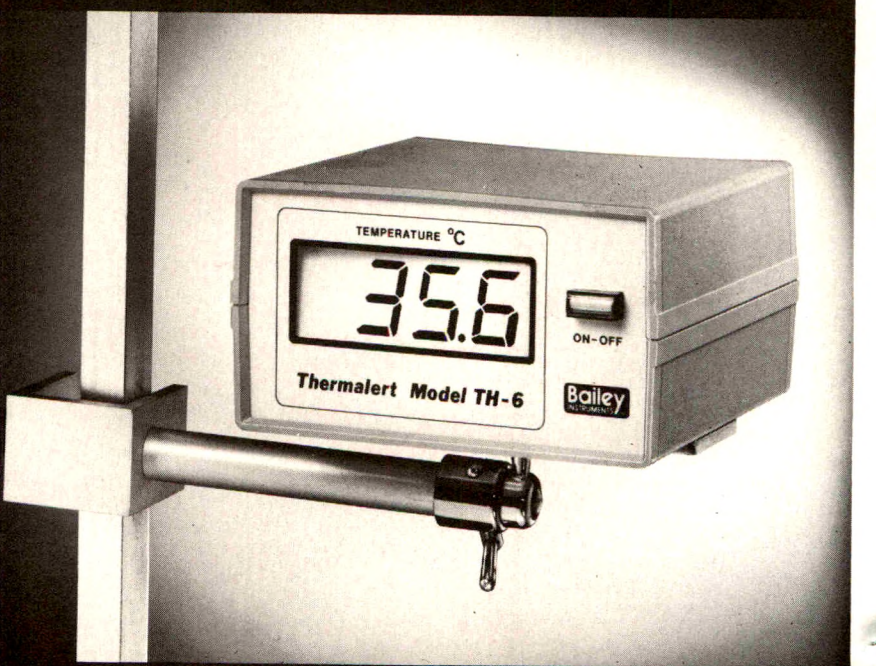
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Thermalert thermometers are intended for continuous temperature monitoring in the OR and for use in specialized techniques such as hypothermic surgery. Thermalerts are as easy to use as glass thermometers, and much easier to read. They can indicate a patient's temperature in less than 20 seconds, which makes them ideal also for rapid screening of large groups such as blood donors.

These thermometers use Bailey type T interchangeable probes and sensors including our 'patient confortable' clinical types, needle probes and micro-probes. They also accept new disposable temperature-sensing stethoscope catheters such as those made by National Catheter Co.

Their digital display enhances reading accuracy and provides early warning of a temperature change, since a movement of 1/10th degree is immediately noticed. Thermalerts are the most advanced monitor thermometers so far devised.

Model TH-6 on Adjustable Stand TTS-1



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	TH-5	TH-6
Temperature Range:	25-45°C	0-50°C
Resolution:	0.1°C	0.1°C
Instrument Accuracy:	0.1°C ±1 digit	0.1°C ±1 digit
Calibration:	Conforms to National Bureau of Standards tables, Monograph 125	
Readout:	1/2" liquid crystal	1" liquid crystal
Battery Life:	700 hours continuous	1500 hours continuous

Use with Bailey Type T probes and microprobes (42 to choose from)

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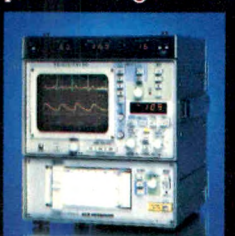
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Until further clinical experience is gained, paracervical block with Marcaine is not recommended. Fetal bradycardia frequently follows paracervical block with some amide-type local anesthetics and may be associated with fetal acidosis. Added risk appears to be present in prematurity, toxemia of pregnancy, and fetal distress.

The obstetrician is warned that severe persistent hypertension may occur after administration of certain oxytocic drugs, if vasopressors have already been used during labor (e.g., in the local anesthetic solution or to correct hypotension).

Solutions containing a vasoconstrictor, particularly epinephrine or norepinephrine, should be used with extreme caution in patients receiving monoamine oxidase (MAO) inhibitors or antidepressants of the triptyline or imipramine types, because severe, prolonged hypertension may result.

Local anesthetics which contain preservatives, i.e., those supplied in multiple dose vials, should not be used for caudal or epidural anesthesia.

Until further experience is gained in children younger than 12 years, administration of Marcaine in this age group is not recommended.

Precautions. The safety and effectiveness of local anesthetics depend upon proper dosage, correct technique, adequate precautions, and readiness for emergencies.

The lowest dosage that gives effective anesthesia should be used in order to avoid high plasma levels and serious systemic side effects. Injection of repeated doses of Marcaine may cause significant increase in blood levels with each additional dose, due to accumulation of the drug or its metabolites or due to slow metabolic degradation. Tolerance varies with the status of the patient. Debilitated, elderly patients and acutely ill patients should be given reduced doses commensurate with age and physical condition.

Solutions containing a vasoconstrictor should be used cautiously in areas with limited blood supply, in the presence of diseases that may adversely affect the patient's cardiovascular system, or in patients with peripheral vascular disease.

Marcaine should be used cautiously in persons with known drug allergies or sensitivities, particularly to the amide-type local anesthetics.

Serious dose-related cardiac arrhythmias may occur if preparations containing a vasoconstrictor such as epinephrine are employed in patients during or following the administration of chloroform, halothane, cyclopropane, trichloroethylene, or other related agents. In deciding whether to use these products concurrently in the same patient, the combined action of both agents upon the myocardium, the concentration and volume of vasoconstrictor used, and the time since injection, when applicable, should be taken into account.

Caution is advised in administration of repeat doses of Marcaine to patients with severe liver disease.

Use in Ophthalmic Surgery. When Marcaine 0.75% is used for retrobulbar block, complete corneal anesthesia usually precedes onset of clinically acceptable external ocular muscle akinesia. Therefore, presence of akinesia rather than anesthesia alone should determine readiness of the patient for surgery.

Adverse Reactions. Reactions to Marcaine are characteristic of those associated with other amide-type local anesthetics. A major cause of adverse reactions to this group of drugs is excessive plasma levels, which may be due to overdosage, inadvertent intravascular injection, or slow metabolic degradation.

Excessive plasma levels of the amide-type local anesthetics cause systemic reactions involving the central nervous system and the cardiovascular system. The *central nervous system effects* are characterized by excitation or depression. The first manifestation may be nervousness, dizziness, blurred vision, or tremors, followed by drowsiness, convulsions, unconsciousness, and possibly respiratory arrest. Since excitement may be transient or absent, the first manifestation may be drowsiness, sometimes merging into unconsciousness and respiratory arrest. Other central nervous system effects may be nausea, vomiting, chills, constriction of the pupils, or tinnitus. The *cardiovascular manifestations* of excessive plasma levels may include depression of the myocardium, blood pressure changes (usually hypotension), and cardiac arrest. In obstetrics, cases of fetal bradycardia have occurred (see Warnings). *Allergic reactions*, which may be due to hypersensitivity, idiosyncrasy, or diminished tolerance, are characterized by cutaneous lesions (e.g., urticaria), edema, and other manifestations of allergy. Detection of sensitivity by skin testing is of doubtful value. Sensitivity to methylparaben preservatives added to multiple dose vials has been reported. Single dose vials without methylparaben are also available.

Reactions following epidural or caudal anesthesia also may include: high or total spinal block; urinary retention; fecal incontinence; loss of perineal sensation and sexual function; persistent analgesia, paresthesia, and paralysis of the lower extremities; headache and backache; and slowing of labor and increased incidence of forceps delivery.

Treatment of Reactions. Toxic effects of local anesthetics require symptomatic treatment; there is no specific cure. The physician should be prepared to maintain an airway and to support ventilation with oxygen and assisted or controlled respiration as required. Supportive treatment of the cardiovascular system includes intravenous fluids and, when appropriate, vasopressors (preferably those that stimulate the myocardium). Convulsions may be controlled with oxygen and intravenous administration, in small increments, of a barbiturate, as follows: preferably, an ultrashort-acting barbiturate such as thiopental or thiamylal; if this is not available, a short-acting barbiturate (e.g., secobarbital or pentobarbital) or diazepam. Intravenous barbiturates or anticonvulsant agents should only be administered by those familiar with their use.

Composition of Solutions.

Marcaine 0.25% — Each ml contains 2.5 mg bupivacaine with NaCl for isotonicity in water for injection.

Marcaine 0.5% — Each ml contains 5 mg bupivacaine with NaCl for isotonicity in water for injection.

Marcaine 0.75% — Each ml contains 7.5 mg bupivacaine with NaCl for isotonicity in water for injection.

In multiple dose vials, each ml also contains 1 mg methylparaben.

In epinephrine, each ml also contains 0.0091 mg epinephrine bitartrate, 0.5 mg sodium bisulfite, 0.001 ml monothioglycerol, 2 mg ascorbic acid, 0.0017 ml 60% sodium lactate, and 0.1 mg edetate calcium disodium.

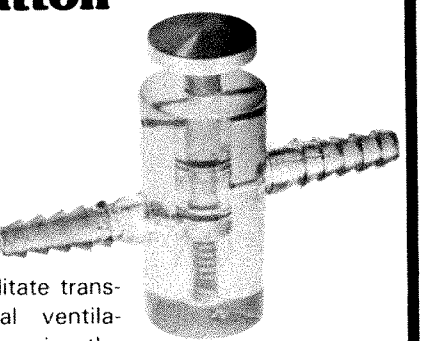
References:

1. Scanlon JW: Obstetric anesthesia as a neonatal risk factor in normal labor and delivery. *Clinics in Perinatology* 1:465-482, 1974.
2. Scanlon JW, Ostheimer GW, Brown WU, et al: Neurobehavioral responses and drug concentrations in newborns after maternal epidural anesthesia with bupivacaine. *Anesthesiology* 45:400-405, 1976.
3. Ostheimer GW: Obstetrics and local anesthetics: Implications for the fetus and newborn. *Anesthesiology Review* 4:17-23, June 1977.

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ANESTH ANALG
1982;61:225-30

Evolution of Single Twitch and Train-of-Four Responses and of Tetanic Fade in Relation to Plasma Concentrations of Fazadinium in Man

Alain A. d'Hollander, MD,* Philippe Duvaldestin, MD,† Claude Delcroix, PhD,‡ Marc Nevelsteen, MD,§ and Jean Marie Desmonts, MD‖

D'HOLLANDER, A. A., DUVALDESTIN, P., DELCROIX, C., NEVELSTEEN, M., AND DESMONTS, J. M.: Evolution of single twitch and train-of-four responses and of tetanic fade in relation to plasma concentrations of fazadinium in man. Anesth Analg 1982;61:225-30.

The evolution of single twitch and train-of-four (2 Hz) responses and tetanic fade (100 Hz) in relation to plasma concentrations of fazadinium was determined during stable anesthesia (fentanyl-N_2O) in six healthy adult patients after a bolus injection of 0.75 mg/kg of fazadinium. The interval between injection and 50% recovery and the corresponding fazadinium plasma concentrations were (mean ± SEM): 47 ± 4 minutes and 1.44 ± 0.18 μg/ml for the single twitch; 66 ± 7 minutes and 1.01 ± 0.10 μg/ml for the train-of-four; and 83 ± 11 minutes and 0.82 ± 0.08 μg/ml for tetanic fade. The results indicate that train-of-four and tetanic fade are more sensitive tests for evaluation of residual neuromuscular block than is measurement of single twitch responses.

Key Words: NEUROMUSCULAR RELAXANTS: fazadinium; MEASUREMENT TECHNIQUES: neuromuscular function.

THE EVOKED response to several modes of frequency stimulation is used in clinical practice to identify and quantify neuromuscular block (1). The responses to single twitch (ST), train-of-four (TOF), or tetanic fade (TF) have been compared for different neuromuscular blocking agents (NMBAs) in previous studies (2-5). However, the simultaneous evolution of the degree of these different methods for evaluation of the degree of neuromuscular blockade has not been characterized in man. The purpose of the present study was to follow simultaneously the time course of recovery of ST, TOF, and TF in the same patients after a single dose of NMBA. Among the NMBAs available, fazadinium (FAZ) was chosen because its intermediate duration (6, 7) of action allows the various tests to be studied during a relatively short period of observation. In addition, the evolution of plasma concentrations of FAZ was studied to describe the relationships between plasma concentration and effect for the different tests studied.

Methods

Six consenting, healthy, middle-aged adult patients (A.S.A. physical status class I to II), showing no clinical or biochemical evidence of hepatic or renal damage, were studied. One hour before anesthesia, all patients received diazepam (10 mg) orally. Anesthesia was induced intravenously with methohexital (1 mg/kg) and fentanyl (5 μg/kg). Once the patient was unconscious, respiration was manually controlled (circle circuit O_2/N_2O 1:1 v/v liters) until endotracheal intubation was performed after the administration of FAZ.

Respiration was controlled mechanically (circle circuit O_2/N_2O 1:2 v/v liters) until the end of the surgical

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This work was supported in part by the Ministère de la Politique Scientifique Belge (Actions concertées).

Received from the Departments of Anesthesiology, Hôpital Brugmann, Université Libre de Bruxelles, Hôpital Bichat, Université Paris VII, and Institut de Recherche Interdisciplinaire en Biologie Humaine et Nucléaire, Université Libre de Bruxelles. Accepted for publication October 26, 1981.

Reprint requests to Dr. d'Hollander, Département Anesthésie, Hôpital Brugmann, 4 pl Van Gehuchten, 1020 Brussels, Belgium.

procedure. Ventilation was adjusted in order to provide normocapnia [end-tidal CO_2 approximately 5.0% ± 0.1% (Datascope 500 CO_2 analyzer) or Pa_{CO_2} 39 ± 3 mm Hg (Corning 175)]. Supplemental doses of fentanyl were given when clinical signs of inadequate analgesia appeared. Thermal loss from the body core and exposed areas was reduced by the use of a water-warming mattress with autoregulation (37°C, rectal temperature monitoring) and surgical drapes.

Monitoring of Neuromuscular Function

Before the start of anesthesia, a displacement transducer (UC3 cell, Statham) fitted with tension attenuator (UL4-10, Statham) and incorporated in a handgrip, was secured with adhesive strips in the right hand of the patient and preloaded to 50 g in order to measure isometric thumb displacement. Two 25-gauge thin-walled needles were placed subcutaneously close to the ulnar nerve at the wrist, and the mechanical activity of the adductor pollicis was elicited by square-wave pulses of 0.2-msec duration and delivered at 0.1 Hz from a Grass S88 stimulator. The stimulation voltage equaled 1.5 times that necessary to evoke a maximal twitch response. The resulting analog signals were amplified and registered on a polygraph recorder (see Fig 1 for schematic illustration of experimental set-up). When a consistent control tension was achieved, after a few minutes, a bolus injection of FAZ, 0.75 mg/kg, was administered.

Every 5 minutes, stimuli were applied to the right hand for 2 seconds at a frequency of 2 Hz, with the same current characteristics as for ST in order to analyze TOF responses as described by Ali, Utting, and Gray (3).

TF was recorded every 20 minutes following the NMBA administration of the left cubital nerve-adductor pollicis group fitted with a similar displacement transducer. The validity of this preparation was checked before each tetanus by stimulating at a frequency of 0.1 Hz. The frequency and the duration of each tetanic stimulation were 100 Hz and 5 seconds, respectively, as proposed by Waud and Waud (8).

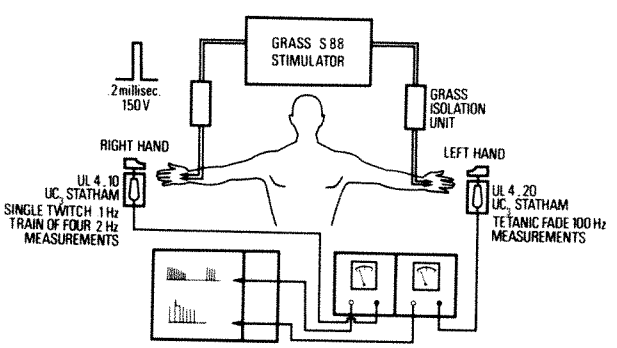


FIG 1. Schematic representation of method for recording single twitch (ST), train-of-four (TOF) (right hand), and tetanic fade (TF) (left hand).

The points corresponding to 25%, 50%, and 75% tetanic fade recovery were obtained by calculation (9) using the observed results and the following equation: percent tetanic fade (f) recovery as a function of time (t) in minutes = $1. - t^p/(t^p + effect_{0.5}{}^p)$ where $effect_{0.5}$ represents the time elapsed to recover a tetanic fade of 50%, p is a parameter representing the slope of this function, and t is the time, expressed in minutes, elapsed form FAZ administration taken at time 0 minutes.

FAZ Plasma Determination

Venous heparinized blood samples were taken at appropriate times to measure FAZ plasma concentrations corresponding to fixed degrees of recovery of ST and TOF signals and during each TF determination period. Total plasma concentrations of FAZ and its metabolites were measured separately by a spectrofluorimetric method (10). In our laboratory, this method is accurate to 0.05 μg/ml.

The decrease of FAZ plasma concentrations measured until the 4th hour after relaxant injection was fitted by a biexponential function according to previous pharmacokinetic studies (11). Following this kinetic analysis, the concentrations corresponding to the calculated TF values of 25%, 50%, and 75% were calculated.

Statistical analysis of the results was performed using bilateral paired signed Wilcoxon sum test (12). Significance was assigned at a level of 5% or less.

Results

The time from FAZ injection to the predetermined recovery level of the studied mechanical tests is shown in Table 1 and Fig 2. ST recovered first and was followed by TOF, which began to recover as soon as ST reached approximately 25%. TF was the last test to recover and it took approximately as long to return to 25% as it took the ST to reach 90%. At the 50% level, these intervals expressed in minutes were (mean ± SEM): 47 ± 4, 66 ± 7, and 83 ± 11 for ST, TOF, and TF, respectively. For each recovery level considered, the recovery times noted for ST were significantly different (Wilcoxon paired signed rank test) from the TOF and TF delays.

Biexponential analysis of changes in plasma FAZ concentrations shows that the $T_{1/2}$ α and $T_{1/2}$ β were 12 ± 3 and 80 ± 15 minutes, respectively. In Table 2

are summarized the FAZ plasma concentrations observed for the different values of the mechanical tests during the recovery period. At the 50% level of ST, TOF, and TF, these concentrations were (mean ± SEM): 1.44 ± 0.18, 1.01 ± 0.10, and 0.82 ± 0.08 μg/ml, respectively. At each level of recovery, the plasma concentrations of FAZ observed during the ST recovery were significantly higher than the concentrations noted for the TOF and TF tests. FAZ concentrations recorded at similar levels of recovery of TOF and TF were also significantly different.

TABLE 1

Delays Observed for Single Twitch (ST), Train-of-Four (TOF), and Tetanic Fade (TF) Recoveries*

	Time elapsed from fazadinium (FAZ) injection at different levels of recovery					Time elapsed between 25% and 75% recovery levels
	10%	25%	50%	75%	90%	
			min			
ST	21 ±3†	35 ±3†	47 ±4†	61 ±6†	71 ±6†	28 ±4†
TOF	39 ±6	51 ±6‡	66 ±7‡	85 ±8‡	112 ±9	35 ±4‡
TF		68 ±9§	83 ±11§	100 ±14§		31 ±6§

* Values are means ± SEM.
† $p < 0.05$, paired Wilcoxon test between ST and TOF.
‡ $p < 0.05$, paired Wilcoxon test between TOF and TF.
§ $p < 0.05$, paired Wilcoxon test between ST and TF.

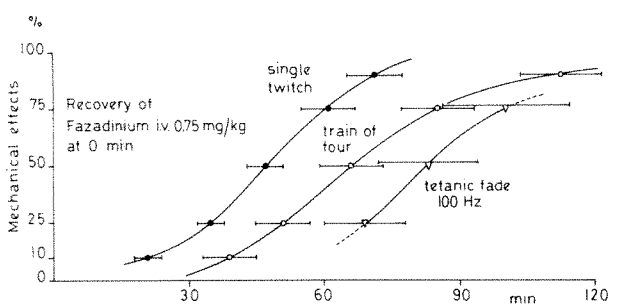


FIG 2. Evolution of recovery of ST, TOF, and TF (mean ± SEM) after bolus injection of fazadinium (FAZ) (0.75 mg/kg IV) at 0 minutes.

Discussion

The aim of this study was to follow simultaneously the waning plasma concentration of FAZ and the recovery curves of a series of mechanical tests investigating different aspects of the interaction of competitive neuromuscular blocking drugs on the function of the human muscular end plate.

The simultaneous study of these various tests is difficult because a series of high frequency stimuli applied to the nerves can themselves affect the analysis of the function of the neuromuscular junction. Fast frequency stimulation is followed by post-tetanic potentiation which impedes the evolution of ST or TOF for several minutes (13, 14). Therefore, monitoring of the neuromuscular block by fast frequency signals and by low frequency signals must be performed on separate neuromuscular units. A similar problem arises in selecting the frequency of repeated measurements of TOF. In fact, Lee (5) noted that a minimum interval of 10 seconds should be observed in order to ensure a good repetition of these signals. The adoption of a frequency of 0.1 Hz for the TOF would have resulted in acetylcholine being released 24 times per minute at the nerve endings. Such a rapid repetition of the TOF made us fear that the ST signal would be affected as Ali and Savarese (15) showed that the dose-response relationship estab-

TABLE 2

FAZ Plasma Concentration Observed for Fixed Degrees of ST, TOF, and TF Recoveries*

	FAZ plasma concentrations at different levels of recovery					FAZ plasma concentration reduction between 25% and 75% recovery levels
	10%	25%	50%	75%	90%	
				μg/ml		
ST	2.82 ±0.22†	1.90 ±0.17†	1.44 ±0.18†	1.08 ±0.12†	0.92 ±0.12†	0.82 ±0.06†
TOF	1.54 ±0.13	1.28 ±0.10‡	1.01 ±0.10‡	0.73 ±0.10‡	0.52 ±0.08	0.57 ±0.02‡
TF		0.99 ±0.08§	0.82 ±0.08§	0.63 ±0.05§		0.36 ±0.07§

* Values are means ± SEM.
† $p < 0.05$, paired Wilcoxon test between ST and TOF.
‡ $p < 0.05$, paired Wilcoxon test between TOF and TF.
§ $p < 0.05$, paired Wilcoxon test between ST and TF.

lished for ST with a stimulation at 0.1 Hz was different at a stimulation frequency of 0.2 Hz, yet the latter frequency only produced a release of acetylcholine 12 times per minute at the motor neuron level. Having selected for our study a 5-minute interval between two successive measurements of TOF, only six supplemental nerve stimuli were added to the ST measurements for each 5-minute period, which appeared relatively unimportant.

The extent of neuromuscular block by competitive agents can also be quantified by the use of tetanic stimulations of varying frequencies as previously reported experimentally (8, 16, 17) and clinically (2, 4, 18). Tetanic stimulation provides a means for assessment of neuromuscular function differing from that provided by low frequency stimulation. Schematically, the tetanic stimulation (30 to 200 Hz) may interfere simultaneously with the release and the mobilization of acetylcholine, whereas low frequency stimulation (less than 0.2 Hz) affects only the pool of acetylcholine immediately releasable (19, 20). Experimentally, Waud and Waud (8) have shown that the absence of tetanic fade at stimulation frequencies of 100 and 200 Hz required a neuromuscular junction having a much lower receptor occupation ratio, of approximately 50% and 30%, respectively, than the levels, generally of 70% to 75%, below which total recovery of ST, TOF, and even tetanus at 30 Hz is obtained. It would appear, therefore, that the use of tetanic stimulation of high frequency provides a simple method of assessing the residual effects of a competitive NMBA. In man, maximum voluntary adduction of the thumb produces muscular activity of a frequency equal to or slightly greater than 50 Hz (21). At this "physiologic" frequency, the tetanic fade recovers at the same time as the single twitch following a single injection of FAZ (18). Consequently, the 50-Hz stimulation frequency is of little use in the evaluation of the long-lasting effects of competitive neuromuscular relaxants. On the other hand, a frequency of 200 Hz appeared to be too high because in man the refractory period of the neuromuscular junction investigated by the twin stimulation technique was in the region of 4 to 6 msec (22). The frequency of 100 Hz selected for this study appeared to be more appropriate for assessing clinically the residual effects of competitive NMBAs.

Our results also clearly show that recoveries of TOF and TF were more prolonged than was ST recovery; at a ST value of 90%, TOF had only reached a value of 55% to 60% and the TF had only reached 25% recovery at the same time. The FAZ plasma concentrations measured at the different stages of recovery of TOF and TF were significantly lower than the corresponding values observed with ST (Table 2). These results indicate that evoked responses to higher frequency stimulation recover at lower FAZ plasma concentrations than do evoked responses associated with the lower frequencies used to measure ST.

By recording the evolution of the plasma concentration of FAZ at the same time as the evolution changes in ST, it is possible by using a recently developed pharmacodynamic mode (23) to define the occupancy ratio of the postsynaptic receptors as a function of time, as suggested by Waud and Waud

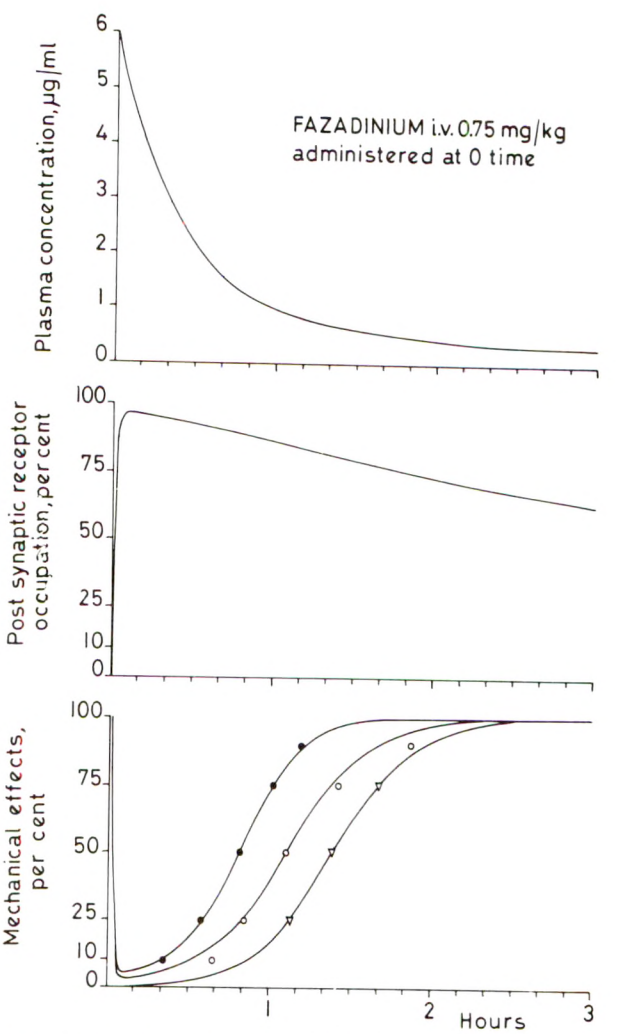


FIG 3. Calculated postsynaptic receptor occupation from observed mean FAZ plasma concentration and mean ST recovery of patients in study, according to pharmacodynamic model developed by d'Hollander and Delcroix (23). Top, calculated mean FAZ plasma concentrations in present patients (biexponential decay). Middle, calculated changes with time in postysynaptic receptor occupation ratios. Bottom, calculated and observed ST (●), TOF (○), and TF (▽) recoveries.

TABLE 3
Comparison of Experimental Receptor Occupancy Ratio Observed in Mammals and Calculated Values of Present Study

	% of mechanical functions at levels of recovery					
	ST		TOF		TF (100 Hz)	
	50%	100%	50%	100%	50%	100%
d-Tubocurarine, in vivo (cat tibialis anterior)*	87†	82	85	69	73	49
d-Tubocurarine, in vivo (cat tibialis anterior)‡					72	50
d-Tubocurarine, in vitro (guinea pig lumbrical)§	85	74				
Fazadinium, in vitro (guinea pig lumbrical)§	88	74				
Fazadinium (man adductor pollicis)‖	89	77	85	71	81	67

* Data from Waud and Waud (16).
† Percentage of receptor occupancy ratio calculated from data of Waud and Waud (8, 16, 30).
‡ Data from Waud and Waud (8).
§ Data from Waud (30).
‖ Data from present study.

(8, 16). Accordingly, we calculated the ranges of the occupancy ratios noted during the recovery of different tests, including TOF and TF (Fig 3). This stimulation does not imply that depression of TOF or TF is exclusively caused by blockade of the postsynaptic receptors. As reported by different authors (24–29), the blockade of presynaptic receptors by non-depolarizing NMBAs probably plays an important role especially in tetanic fade phenomenon. This simulation shows that the recovery of ST, TOF, and TF takes place only when the occupancy ratios of the postsynaptic receptors are 77%, 71%, and 67%, respectively. These calculated values for FAZ are close to those obtained experimentally (see Table 3, for comparison). With the modes of stimulation used in this clinical study, recovery of differing mechanical tests measuring neuromuscular function in the presence of a competitive neuromuscular relaxant, fazadinium, was delayed depending upon the type of stimuli used. For comparable levels of recovery, both the plasma concentrations and the delays in recovery recorded for ST were significantly different from those noted from TOF and TF. TF, using 100 Hz stimuli, appeared to be more appropriate than ST or TOF for estimating residual neuromuscular block following administration of competitive neuromuscular relaxants in man.

ACKNOWLEDGMENTS

The authors are grateful to Professor J. Primo-Dubois, Chairwoman, Department of Anesthesia, Brugmann Hospital, for her cooperation in organizing the clinical sessions and to Professor W. C. Bowman, Chairman, Department of Physiology and Pharmacology, University of Strathclyde, Scotland, for his help in the preparation of the manuscript.

REFERENCES

1. Ali HH, Savarese JJ. Monitoring of neuromuscular function. Anesthesiology 1976;45:216–27.
2. Gissen AJ, Katz RL. Twitch, tetanus and posttetanic potentiation as indices of nerve-muscle function. Anesthesiology 1969; 30:481–7.
3. Ali HH, Utting JE, Gray TC. Quantitative assessment of residual anti-depolarizing block (part I). Br J Anaesth 1971;43:473–7.
4. Heisterkamp DB, Skovsted P, Cohen PJ. The effects of small incremental doses of d-tubocurarine on neuromuscular transmission in anesthetized man. Anesthesiology 1969;30:500–5.
5. Lee C. Train-of-four quantification of competitive neuromuscular block. Anesth Analg 1975;54:649–53.
6. Bolger L, Brittain RT, Jack D, et al. Short-lasting competitive neuromuscular blocking activity in a series of azobis arylimidazo (1,2-a)pyridium dihalides. Nature 1972;238:354–5.
7. Camu F, d'Hollander A. Neuromuscular blockade of fazadinium bromide (AH 8165) in renal failure patients. Acta Anaesthesiol Scand 1978;22:221–7.
8. Waud BE, Waud BR. The relation between tetanic fade and receptor occlusion in the presence of competitive neuromuscular block. Anesthesiology 1971;35:456–64.
9. Berman M, Weiss M. Users manual for SAAM (simulation, analysis and modeling), SAAM 25 version. Bethesda, MD: National Institutes of Health Editions, 1971.
10. Pastorino AM. Fluorimetric determination and pharmacokinetic studies of fazadinium bromide in dogs. Arzneim Forsch 1978;28:1728–30.
11. Duvaldestin Ph, Henzel D, Demetriou M, Desmonts JM. Pharmacokinetics of fazadinium in man. Br J Anaesth 1978;50:773–7.
12. Wilcoxon F. Individual comparison by ranking methods. Biometrics 1945;1:80–3.
13. Liley AW, North KA. An electrical investigation of effects of repetitive stimulation on mammalian neuromuscular junction. J Neurophysiol 1953;16:509–27.
14. Feldman SA. The termination of action of relaxants. In: Feldman SA, ed. Muscle relaxants, London: WB Saunders, 1973: 65–71.
15. Ali HH, Savarese JJ. Stimulus frequency and dose-response curve to d-tubocurarine in man. Anesthesiology 1980;52:36–40.
16. Waud BE, Waud BR. The relation between the response to "train of four" stimulation and receptor occlusion during competitive neuromuscular block. Anesthesiology 1972;37:413–6.
17. Bowman WC, Webb SN. Tetanic fade during partial transmission failure produced by non depolarizing neuromuscular blocking drugs in the cat. Clin Exp Pharmacol Physiol 1976;3: 545–55.

18. d'Hollander AA, Delcroix C. Predicting the duration of action on non-depolarizing curares. In: Curares and curarisation. Amsterdam: Excerpta Medica, 1980:209–24.
19. Elmquist D, Quastel DM. A quantitative study of end-plate potentials in isolated human muscle. J Physiol (Lond) 1965; 178:505–29.
20. Miller RD. Factors affecting the action of muscle relaxants. In: Katz R, ed. Muscle relaxants. New York: North Holland Publishing Co, 1975:163–91.
21. Merton PA. Voluntary strength and fatigue. J Physiol 1954; 123:553–64.
22. Lee C, Barnes A, Yang E, Katz RL. Neuromuscular facilitation during train of four and tetanic stimulation in healthy volunteers: observations with half-refractory paired responses. Br J Anaesth 1977;49:555–9.
23. d'Hollander AA, Delcroix C. An analytical pharmacodynamic model for non-depolarizing neuromuscular blocking agents. J Pharmacokinet Biopharm 1981;9:27–40.
24. Lilleheil G, Naess K. A presynaptic effect of d-tubocurarine in the neuromuscular junction. Acta Physiol Scand 1961;52:120–36.
25. Hubbard JI, Wilson DF, Miyamoto M. Reduction of transmitter release by tubocurarine. Nature 1969;223:531–3.
26. Galindo A. The role of prejunctional effects in myoneural transmission. Anesthesiology 1972;36:598–608.
27. Lee C, Chen D, Katz RL. Characteristics of non depolarizing neuromuscular block. 1). Post-junctional block by alpha-bungarotoxin. Can Anaesth Soc J 1977;24:212–9.
28. Su PC, Wen-Huey LS, Rosen AD. Pre- and postsynaptic effects of pancuronium at the neuromuscular junction of the mouse. Anesthesiology 1979;50:199–204.
29. Bowman WC. Prejunctional and postjunctional cholinoceptors at the neuromuscular junction. Anesth Analg 1980;59:935–43.
30. Waud BE. Kinetic analysis of the AH 8165-receptor interaction at the mammalian neuromuscular junction. Anesthesiology 1977;46:94–6.

Valve Replacement without Preoperative Cardiac Catheterization

During the year 1978, the decision to perform cardiac catheterization in patients with valvular heart disease was delayed until clinical and noninvasive assessment had been completed. As a result, 184 patients underwent operation without invasive studies, and 59 had elective catheterization. Another 62 patients were referred during the same period for valve replacement after routine catheterization had been performed elsewhere. Age, sex distribution, symptoms, and cause of valve disease were similar in all three groups, although emergencies and second operations were managed more frequently without catheterization. In all patients the preoperative diagnosis was confirmed, and no unexpected pathologic process was encountered. Operative mortality was the same in all three groups, and after two years of follow-up there was no difference in survival or symptoms. No uncorrected valve lesions became apparent in uncatheterized patients. The authors conclude that routine catheterization is unnecessary before valve replacement but can be reserved for specific indications in some patients. *(St. John-Sutton MG, St. John-Sutton M, Oldershaw P, et al. Valve replacement without preoperative cardiac catheterization. N Engl J Med 1981;305:1233–8)*
(See also—Brandenburg RO. Editorial: No more routine catheterization for valvular heart disease? N Engl J Med 1981;305:1277–8)

ANESTH ANALG
1982;61:231-5

Intrapulmonary Shunting during Induced Hypotension

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CASTHELY, P. A., LEAR, S., COTTRELL, J. E., AND LEAR, E.: Intrapulmonary shunting during induced hypotension. Anesth Analg 1982;61:231-5.

The effect of sodium nitroprusside (SNP) and nitroglycerin (TNG) on pulmonary shunting ($\dot{Q}s/\dot{Q}t$) in 14 consenting adults [nine with normal lung function and five with chronic obstructive pulmonary disease (COPD)] was studied under general anesthesia. $\dot{Q}s/\dot{Q}t$ significantly increased ($p < 0.005$) from 5.19% to 8.81%, whereas pulmonary arterial pressure (PAP) decreased from 18.5 to 8 torr ($p < 0.005$) and pulmonary vascular resistance (PVR) decreased from 235 to 147.75 dynes · sec/cm^5 ($p < 0.025$) when SNP was administered to patients with normal lung function. Nitroglycerin increased $\dot{Q}s/\dot{Q}t$ from 5.13% to 6.19% ($p < 0.005$), whereas PAP decreased from 18 to 10 torr ($p < 0.005$) and PVR decreased from 237 to 162.6 dynes · sec/cm^5 ($p < 0.025$) in these patients. In patients with COPD, SNP and TNG produced no significant changes in $\dot{Q}s/\dot{Q}t$, PAP, or PVR. Cardiac output remained unchanged in both groups of patients. Various mechanisms to explain these results can be postulated. When hypotension is induced in patients with normal pulmonary function, PAP decreases and the effect of gravity puts more blood through dependent areas where most of the shunt units are. In patients with COPD, destructive vascular changes increase PAP, preventing vasodilators from decreasing PVR. In addition, dilation of hypoxic pulmonary vasoconstriction (if present) by SNP and TNG will occur independent of the two previously mentioned mechanisms. These results provide evidence that SNP- and TNG-induced hypotension may cause significant impairment in pulmonary gas exchange in patients with normal lung function. In patients with COPD pulmonary gas exchange is not affected after deliberate hypotension with SNP or TNG.

Key Words: LUNG: shunting; ANESTHETIC TECHNIQUES, Hypotensive: nitroprusside, nitroglycerin.

ALTHOUGH investigators (1-6) agree that general anesthesia interferes with pulmonary gas exchange, the role of pulmonary shunting in the evolution of intraoperative hypoxemia has not been clearly delineated.

Hypotensive anesthesia has been used to decrease blood loss and facilitate surgery during procedures such as major head and neck operations, clipping of intracerebral aneurysms, removal of arteriovenous malformations, total hip replacement, Harrington rod insertion, and radical cancer surgery. Studies (7-10) have shown impairment of pulmonary gas exchange following the use of vasodilators for deliberate hypotension.

Our interest has focused on increased intrapulmonary shunting as the pathophysiologic mechanism behind this hypoxemia. Accordingly, we decided to study the influence of sodium nitroprusside (SNP) and nitroglycerin (TNG) on shunt fraction in a group of patients during general anesthesia and surgery.

The study protocol was submitted to and approved by the Human Research Committee and informed consent was obtained from each patient.

Methods

We studied 14 adult surgical patients (Table 1), 26 to 56 years old, who were scheduled for surgical procedures under deliberate hypotensive anesthesia. Patients were divided into two groups according to pulmonary function and chest roentgenograms. Group I consisted of nine patients with normal lungs;

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Received from the Departments of Anesthesiology, Downstate School of Medicine, Brooklyn; and Mount Sinai School of Medicine, New York; and the Department of Medicine, Albert Einstein College of Medicine, Bronx, New York. Accepted for publication October 27, 1981. Presented in part at the Annual Meeting of the Society of Neurosurgical Anesthesia and Neurologic Supportive Care, October 19, 1979, San Francisco, California.

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TABLE 1

Sex, Age, Surgical Procedure, Together with Preoperative Blood Pressure (BP), Ratio of Forced Expiratory Volume to Forced Vital Capacity (FEV/FVC), Pa_{O_2} and Pa_{CO_2} in Patients with Normal Lungs (Group I) and in Patients with Chronic Obstructive Pulmonary Disease (COPD, Group II)

Sex	Age	Procedure	BP	$\overline{BP}$ during hypotension	VC*	FEV/FVC	Pa_{CO_2}	Pa_{O_2}
	yr		*torr*				*torr*	
Group I								
F	41	Mastectomy	149/70	70.0	94	81.5	37	87
F	26	Reduction mammoplasty	120/80	60.0	96	82.0	38	90
F	29	Reduction mammoplasty	110/70	55.0	97	2.1	40	92
F	48	Mastectomy	130/90	60.0	95	80.5	39	85
M	45	Clipping cerebral aneurysm	165/90	67.5	93	82.1	35	81
F	39	Clipping cerebral aneurysm	160/90	65.0	94	81.7	38	80
M	38	Left radical neck dissection	130/90	60.0	95	80.75	37	86
F	26	Reduction mammoplasty	110/80	60.0	96	81.5	38	90
F	49	Mastectomy	120/90	62.0	92	81.0	39	85
Group II								
M	48	Clipping cerebral aneurysm	160/90	65.0	74	40.5	47	72
F	52	Mastectomy	140/90	70.0	77	41.0	45	70
F	47	Axillary node dissection	130/70	60.0	72	38.5	44	69
M	48	Groin dissection	140/80	65.5	70	37.5	49	66
M	56	Clipping cerebral aneurysm	170/90	65.0	76	39.8	44	71

* % predicted.

group II consisted of five patients with chronic obstructive pulmonary disease (COPD) and mild carbon dioxide retention. Intramuscular morphine, 0.1 mg/kg, and atropine, 0.4 mg, were administered 1 hour before surgery. A 20-gauge catheter was inserted into the radial artery to facilitate arterial blood gas sampling and to monitor blood pressure before induction of anesthesia and throughout the procedure. A #7 French triple-lumen balloon-tipped, thermodilution Swan-Ganz type catheter was introduced through the right internal jugular vein into the pulmonary artery for determination of pulmonary arterial pressures, cardiac output, and mixed venous sampling. Cardiac output was determined using an Edwards computer model 9520A and the electric injector.

Anesthesia was induced with thiopental, 3 to 4 mg/kg, followed by pancuronium, 0.1 mg/kg, to facilitate endotracheal intubation. Anesthesia was maintained with 60% nitrous oxide in oxygen, fentanyl, and additional pancuronium as needed. Patients were mechanically ventilated with an Air Shields Ventimeter ventilator, starting at 10 ml/kg and a rate of 10 breaths per minute. Arterial blood gases were monitored and minute volume adjusted as necessary to maintain an arterial CO_2 level between 35 and 40 torr in group I and 40 to 45 torr in group II patients at all times during the study.

Nitroglycerin was administered to maintain mean arterial blood pressure at two thirds of the patients' preoperative base line for 30 minutes. Blood pressure (BP) was then allowed to return to control (preoperative) levels for 30 minutes before SNP was administered in a similar manner.

Arterial blood samples were collected anaerobically in heparinized syringes for measurement of gas tensions after the induction of anesthesia, 30 minutes after anesthesia stabilized, 30 minutes after the desired hypotension with TNG, and 30 minutes after TNG was discontinued and BP restored to base line value. The same sequence was used during hypotension with SNP.

A Radiometer blood gas analyzer (model ABL 1) was used for determination of arterial blood gas tensions. The oxygen tension (Pa_{O_2}) indicated by the oxygen (O_2) electrode of the ABL 1 machine was corrected by a special nomogram based on a reference method using tonometry of blood (11-13).

Shunt was calculated with an improved program Texas Instruments 59 computer using the formula pulmonary shunting $(\dot{Q}s/\dot{Q}T) = Cc_{O_2}2 - Ca_{O_2}/Cc_{O_2} - C\bar{V}_{O_2}$ (see "Appendix," equation 1) in which the solubility of O_2 in blood was corrected for temperature and hemoglobin content (14).

Results were analyzed statistically using Student's

t-test for paired data. Values were considered statistically significant when the p value was <0.005 and were expressed in means ± standard error.

Results

Data are shown in Tables 2 and 3. The mean dose of TNG infused was 1.6 μg/kg/min; the mean dose of SNP was 3.5 μg/kg/min.

Shunt

Patients in group I had a significant increase in shunt fraction after TNG and SNP administration; the increased shunt was greater after SNP than after TNG. Patients in group II had no significant change in shunt fraction after either drug.

Cardiac Output

In both groups of patients, cardiac output was maintained.

Pulmonary Vascular Resistance

There was a significant decrease in pulmonary vascular resistance (PVR) in patients in group I after TNG and SNP. Patients in group II had no significant changes in PVR (see "Appendix," equation 2).

TABLE 2
Hemodynamic Effects of Intravenous Nitroglycerin (TNG)*

	Group	Before TNG	30 min after desired hypotension	30 min after TNG
$\dot{Q}s/\dot{Q}t$ (%)	I	5.13 ± 0.48	6.59 ± 0.56†	5.19 ± 0.51
	II	8.12 ± 0.97	8.37 ± 0.74	8.14 ± 0.86
CO (L/min)	I	4.15 ± 0.26	4.22 ± 0.15	4.17 ± 0.19
	II	3.78 ± 0.34	3.82 ± 0.27	3.75 ± 0.27
PVR (dynes·sec/cm^5)	I	237.0 ± 4.0	162.6 ± 3.0†	235 ± 3
	II	318.3 ± 9.7	307.4 ± 12.7	317.5 ± 8.6
PAP (torr)	I	18 ± 1.15	10 ± 1†	18.5 ± 1
	II	28 ± 3.0	26 ± 1	27.5 ± 2
HR (beats/min)	I	84 ± 1.2	87.5 ± 2.1	85 ± 2.0
	II	85 ± 0.5	89.6 ± 1.7	85 ± 1.5
Pa_{O_2} (torr)	I	146 ± 11.5	105 ± 3.5	140 ± 9.5
	II	105 ± 10.5	119 ± 9.25	100.8 ± 8.75
Pa_{CO_2} (torr)	I	35.0 ± 3.5	35.5 ± 1.5	35 ± 2.0
	II	36.5 ± 2.5	36 ± 2	36.5 ± 2.5

* Values are means ± SEM. Abbreviations used are: $\dot{Q}s/\dot{Q}t$, pulmonary shunting; CO, cardiac output; PVR, pulmonary vascular resistance; PAP, pulmonary arterial pressure; HR, heart rate.
† Significant at $p < 0.005$.

TABLE 3
Hemodynamic Effects of Intravenous Sodium Nitroprusside (SNP)*

	Group	Before SNP	30 min after desired hypotension	30 min after SNP
$\dot{Q}s/\dot{Q}t$ (%)	I	5.19 ± 0.48	8.81 ± 0.37†	5.25 ± 0.47
	II	8.14 ± 0.97	8.41 ± 0.82	8.15 ± 0.80
CO (L/min)	I	4.17 ± 0.26	4.13 ± 0.28	4.16 ± 0.20
	II	3.75 ± 0.34	3.75 ± 0.75	3.74 ± 0.40
PVR (dynes·sec/cm^5)	I	235.0 ± 4.0	147.75 ± 3.5†	229 ± 2.75
	II	317.3 ± 9.7	300.3 ± 9.6	305 ± 8.0
PAP (torr)	I	18.5 ± 1.15	8 ± 0.75†	16 ± 0.86
	II	27.5 ± 3.0	25 ± 1.25	29 ± 1.5
HR (beats/min)	I	84 ± 1.2	108.0 ± 1.9†	87 ± 1.5
	II	85 ± 0.5	98.90 ± 2.7†	84 ± 1.8
Pa_{O_2} (torr)	I	135 ± 10.5	92.3 ± 0.75	145 ± 7.5
	II	110 ± 3.0	105.0 ± 2.5	100.5 ± 3.5
Pa_{CO_2} (torr)	I	35.5 ± 3.0	36 ± 1.75	35 ± 2.5
	II	36 ± 3.5	35 ± 2.5	37 ± 3

* Values are means ± SEM. Abbreviations are defined in footnote to Table 2.
† Significant at $p < 0.005$.

Pulmonary Arterial Pressure

There was a significant decrease in pulmonary arterial pressure (PAP) in patients in group I after either TNG or SNP; patients in group II did not have any significant decrease in PAP.

Heart Rate

SNP was associated with a significant increase in heart rate in both groups of patients when BP was decreased to two thirds of its preoperative level. TNG did not significantly affect heart rate in either group when BP was decreased to two-thirds of preoperative level.

All values returned to normal within 30 minutes after drug administration terminated.

Discussion

Anesthesia and surgery are associated with factors that tend to cause pulmonary hypoxemia. Constant volume ventilation may be associated with microatelectasis; surgical position and the use of muscle relaxants during anesthesia are responsible for a reduction in functional residual capacity (FRC) (15, 16). Changes in FRC and closing volume during surgery contribute to airway closure and trapping of gas in alveoli distal to the closure (17). The pulmonary hypoxemia encountered is offset to a degree by reflex pulmonary vasoconstriction (18, 19), which diverts blood to adequately ventilated lung.

The autoregulatory hypoxic pulmonary vasoconstrictive reflex has been demonstrated in vivo not only in humans and animals and in lung preparations but also in in vitro vessel preparations with intact perivascular tissue. Inhibition of hypoxic pulmonary vasoconstriction has been noted that hypocapnia, pulmonary hypertension (cor pulmonale), calcium antagonists, adrenergic drugs, vasodilators, and inhalation anesthetics (3, 4, 18, 20).

Depression of hypoxic pulmonary vasoconstriction is hypothesized as being one of the pathophysiologic mechanisms whereby increased shunt occurs after the administration of vasodilator drugs during general anesthesia. Interference with the hypoxic pulmonary vasoconstrictor reflex by the administration of SNP and TNG has been demonstrated in dogs (19). In these studies one lung was ventilated with nitrogen while the other lung was normally ventilated. Intravenous xenon-133 was administered and internal chest counters measured perfusion redistribution. Pulmonary vascular resistance was not significantly altered by SNP and TNG but perfusion, normally diverted from the hypoxic lung, increased. Colley and Cheney (21) studied 10 dogs in which they collapsed an entire lung. Following the infusion of SNP, they found an increase in shunt, no increase in oxygen content, and a decrease in PVR in the atelectatic lung with no change in PVR in the ventilated lung. Hodges, et al (22) demonstrated that SNP in conjunction with moderately increased airway pressure did not affect shunt or cardiac output while providing blood pressure reductions of 40% to 50%. High levels of airway pressure (10 cm H_2O) during SNP infusion caused a decrease not only in blood pressure but also in shunt and cardiac output.

Our findings of increased shunt in normal patients after SNP and TNG are in agreement with previous reports (7, 20, 23). Cardiac output did not, however, change significantly in either patients with normal lungs (group I) or in patients with COPD (group II). Significant decreases in PVR and PAP, occurred, nevertheless, in patients in group I following SNP and TNG administration. On the other hand, in patients in group II neither shunt nor PVR or PAP changed significantly with either SNP or TNG.

These results may be explained by the fact that when hypotension is induced in patients with normal pulmonary function, dilation of the pulmonary vascular bed increases the blood flowing to the dependent areas of the lung where most of the shunt units are. This increases flow through pulmonary capillaries that normally are closed, thereby increasing ventilation:perfusion abnormalities. Furthermore, a low ventilation:perfusion ratio in patients with normal lungs encourages hypoxic pulmonary vasoconstriction. The administration of SNP and TNG could have blunted this reflex, thereby increasing the blood flow to nonventilated alveoli. This increase of shunting was greater following SNP, thus supporting the observation by Hales et al (20) that SNP inhibits hypoxic pulmonary vasoconstriction more than TNG does.

Patients with COPD have a decrease in the total cross-sectional area of the pulmonary vascular bed due to anatomic changes from chronic constriction of smooth muscle in response to alveolar hypoxia. Pulmonary artery pressure remains elevated even after administration of SNP and TNG because of the irreversible alteration of the pulmonary bed; therefore an increase of blood flowing to nonventilated or underventilated alveoli is prevented. Benumof and Wahrenbrock (4) have shown that these patients have blunted hypoxic pulmonary vasoconstriction reflexes because of fixed PAP increases.

In conclusion, both SNP and TNG produced significant increases in shunt in anesthetized patients with normal lungs. Patients with COPD did not exhibit similar increases. Shunt in patients with normal lungs was greater following SNP than TNG because of its more intense vasodilator effect. The effects of SNP and TNG on shunting appear to depend on the extent of changes in pulmonary vasomotor tone caused by ventilation:perfusion abnormality and on the presence of increased pressure in the pulmonary vascular bed in patients with COPD. Changes in pulmonary vasculature may be responsible for the absence of shunt in patients with COPD.

Appendix

Shunt was calculated using the following formula:

$$\frac{\dot{Q}s}{\dot{Q}T} = \frac{Cc_{O_2}2 - Ca_{O_2}}{Cc_{O_2} - C\bar{V}_{O_2}} \quad (1)$$

where $\dot{Q}s/\dot{Q}T$ is venous admixture, Cc_{O_2} is oxygen content in pulmonary end-capillary blood, Ca_{O_2} is oxygen content of arterial blood, and $C\bar{V}_{O_2}$ is oxygen content of mixed venous blood.

Pulmonary vascular resistance was calculated using the following formula:

$$PVR = \frac{MPAP - MLAP}{Q} \quad (2)$$

where PVR is pulmonary vascular resistance, MPAP is mean pulmonary artery pressure, MLAP is mean left atrial pressure, and Q is cardiac output.

REFERENCES

1. Marshall B, Wyche MG Jr. Hypoxemia during and after anesthesia. Anesthesiology 1072;37:178–209.
2. Rehder K, Sessler AD, Marsh HM. General anesthesia and the lung. Am Rev Respir Dis 1975;112:541–63.
3. Sykes MK, Loh L, Seed RF, Kafer ER, Chakrabarti MK. The effect of inhalational anaesthesia on hypoxic pulmonary vasoconstriction and pulmonary vascular resistance in the perfused lungs of the dog and cat. Br J Anaesth 1972;44:776–88.
4. Benumof JL, Wahrenbrock EA. Blunted hypoxic pulmonary vasoconstriction by increased lung vascular pressure. J Appl Physiol 1975;38:846–50.
5. Stone JG, Sullivan SF. Halothane anesthesia and pulmonary shunting. Anesthesiology 1972;37:582–7.
6. Stone JG, Khambatta JG, Donham RT, Sullivan SF. Pulmonary shunting during anaesthesia in man. Can Anaesth Soc J 1975;22: 647–52.
7. Fahmy NR. Nitroglycerin as a hypotensive drug during general anesthesia. Anesthesiology 1978;49:17–20.
8. Lawson NW, Thompson DS, Nelson CL, Flacke JW, Seifen AB. A dosage nomogram for sodium nitroprusside induced hypotension under anesthesia. Anesth Analg 1976;55:574–81.
9. Eckenhoff JE, Enderby GEH, Larson A, Edridge A, Judevine DE. Pulmonary gas exchange during deliberate hypotension. Br J Anaesth 1963;35:750–8.
10. Askrog VF, Pender JW, Eckenhoff JE. Changes in physiological deadspace during deliberate hypotension. Anesthesiology 1964;25:744–51.
11. Oeseburgh B, Kwant G. Inaccuracy of oxygen electrode system. Anesthesiology 1979;51:368.
12. Kokholm G, Van Schaick J. An analysis and discussion of ABL 1 and ABL 2 differences. Manual Reference Book, Radiometer A/S Emdrupvij 72 DK-2400, Copenhagen, 1979.
13. Andersen PK, Brinklov MM, Stokke DB, Hole P, Rosendal T. Inaccuracy of oxygen electrodes at high blood oxygen tensions. Anesthesiology 1978;49:61–2.
14. Siegel M, Ramanathan S, Chalon J, Turndorf H. An improved program to calculate intrapulmonary shunting. Crit Care Med 1979;7:282–3.
15. Hickey RF, Vesick WD, Fairley HB. Effects of halothane anesthesia on functional residual capacity and alveolar arterial oxygen tension difference. Anesthesiology 1973;38:20–4.
16. Laws AK. Effects of induction of anaesthesia, and muscle paralysis on functional residual capacity. Can Anaesth Soc J 1968;15:325–31.
17. Don HF, Wabha WM, Craig DB. Airway closure, gas trapping and the functional residual capacity during anesthesia. Anesthesiology 1972;36:533–9.
18. Bjertnaes LJ. Hypoxia-induced vasocostriction in isolated perfused lungs exposed to injectable or inhalation anaesthetics. Acta Anaesthesiol Scand 1977;21:133–47.
19. Stone JG, Sullivan SF. Pulmonary shunting during alveolar hypoventilation in the dog. Anesthesiology 1975;42:443–50.
20. Hales C, Slate J, Westphal D. Blockade of alveolar hypoxic vasoconstriction by sodium nitroprusside and nitroglycerin. Am Rev Respir Dis 1977;115–335.
21. Colley PS, Cheney PW. Sodium nitroprusside increases in $\dot{Q}s/\dot{Q}t$ in dogs with regional atelectasis. Anesthesiology 1977;47: 338–41.
22. Hodges MR, Stanley TH, Johansen RK. Pulmonary shunting and cardiovascular responses to CPAP during nitroprusside induced hypotension. Anesthesiology 1977;46:339–41.
23. Stone JG, Khambatta HJ, Matteo RS. Pulmonary shunting during anesthesia with deliberate hypotension. Anesthesiology 1976;45:508–15.

ANESTH ANALG
1982;61:236–40

Epidural Morphine for Postoperative Analgesia: A Double-Blind Study

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LANZ, E., THEISS, D., RIESS, W., AND SOMMER, U.: Epidural morphine for postoperative analgesia: a double-blind study. Anesth Analg 1982;61:236–40.

Postoperative analgesia and the side effects of epidurally injected morphine were investigated in a double-blind study. Following lumbar epidural anesthesia for orthopedic operations, 174 patients received, in a randomized, double-blind fashion, either 0.1 mg/kg of morphine epidurally, 0.1 mg/kg of morphine intramuscularly, or saline epidurally at the end of surgery. Following epidural morphine, postoperative pain was less frequent, less intense and of shorter duration, use of analgesics and sedative was less frequent; and the postoperative feeling of well-being was rated better than after systemic morphine or epidural saline. These effects were more frequent when bupivacaine was used for operative epidural anesthesia than when mepivacaine was used. The results were age independent. Side effects following epidural morphine included pruritus and disturbances of micturition. Nausea, vomiting, fatigue, and headache were of comparable frequency in the three groups.

Key Words: ANESTHETIC TECHNIQUES: epidural; ANALGESICS: morphine; PAIN: postoperative.

IN SPITE OF numerous recent investigations on use of epidural opiates (1–18), there are still questions that need to be addressed regarding their postoperative analgesic efficacy. How frequent, intensive, and long-lasting is the analgesic effect of epidural morphine? Is the analgesic effect of epidural morphine influenced by the local anesthetic used for epidural anesthesia? What are the side effects of this technique and how common are they? To answer these questions we used a double-blind study to investigate postoperative analgesic effect and side effects following equal doses of epidural or intramuscular morphine or an epidural saline placebo.

Methods

Following their informed consent, 174 patients were given lumbar epidural anesthesia for orthopedic surgery of the lower extremities. After identification of one epidural space at L3–4, a catheter was advanced 2.5 cm into the epidural space. Mepivacaine 2% or bupivacaine 0.5% was then injected, depending on the expected duration of the operation.

Before the study began, patients were numbered according to their operating order and assigned to one of three groups.

Patients in group 1 received epidural morphine: morphine hydrochloride, 0.1 mg/kg, in 15 ml of normal saline was injected epidurally and normal saline, 0.01 ml/kg, was injected intramuscularly. Patients in group 2 received intramuscular morphine: morphine hydrochloride, 0.1 mg/kg, was given intramuscularly and normal saline, 15 ml, was given epidurally. Patients in group 3 received saline placebo: normal saline, 15 ml, was given epidurally and normal saline, 0.01 ml/kg, was given intramuscularly. In each group, patients received one of the combinations epidurally and intramuscularly at the end of surgery under double-blind conditions.

Patients were carefully monitored in the recovery room until the morning of the first postoperative day. If the patients complained of pain, they received as analgesics pentazocine or piritramide IM or metamizol, added to the intravenous infusion. Occasionally the sedative promethazine was combined with the analgesics. Ward personnel were not aware of the patient's randomized group. Postoperative records included blood pressure, pulse rate, pain (none, mild, moderate, severe, very severe), analgesics and sedative (dose, time of administration), micturition (spontaneous, following carbachol, catheterization, volume, time), and any special observations.

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Received from the Department of Anesthesiology of the Johannes Gutenberg-Universität Mainz, Langenbeckstrasse 1, 6500 Mainz, West Germany. Accepted for publication October 27, 1981. Results of this study were evaluated in the doctoral dissertation of W. Riess.
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On the afternoon of the first postoperative day, one anesthesiologist, also unaware of the patient's randomized group, interviewed each patient. He recorded the following information: (*a*) general patient data (age, weight, sex); (*b*) data on the epidural anesthesia (local anesthetic used, together with dose, time of injection, and reinjections, if any); (*c*) time of the morphine or placebo injection; (*d*) time of onset of severe postoperative pain; (*e*) subjective postoperative pain rating (1, no pain; 2, mild pain; 3, moderate pain; 4, severe pain; 5, very severe pain) from the end of surgery to the time of interview; (*f*) subjective sleep rating during the first postoperative night (good, moderate, bad); (*g*) side effects (disturbed micturition, pruritus, nausea, vomiting, fatigue, headache, etc); (*h*) subjective rating of feeling of well-being. Only when the recall appeared reliable and corresponded with the postoperative records were data recorded.

The data were recorded on punched cards and statistically evaluated. Frequency distribution and comparisons by analysis of variance, *t*-test, and chi-square test were determined.

Results

Patients in each of the three groups were similar in age, male/female ratio, and body weight. When morphine was administered, the doses were similar (Table 1). The frequency with which mepivacaine and bupivacaine were used for epidural anesthesia, the operative site, and the frequency of complete analgesia at that time were also similar (Table 2).

Postoperative Analgesia

The frequency with which patients experienced no postoperative pain at the site of surgery was significantly greater following epidural morphine than following intramuscular morphine or epidural saline (Table 3).

The severity of pain at the site of surgery during the first 24 hours following surgery was less following epidural morphine than following intramuscular morphine or epidural saline. Those patients having postoperative pain experienced its onset significantly later after epidural morphine than after intramuscular morphine or epidural saline (Table 3). Following epidural morphine, more patients slept well and fewer patients slept poorly (Table 3).

The patients' subjective feelings of well-being during the first 24 hours were significantly better following epidural morphine than following intramuscular morphine or epidural saline (Table 4).

TABLE 1

Patient Data and Morphine Dosage

	Epidural morphine (n = 57)	Intramuscular morphine (n = 57)	Epidural saline (n = 60)
Age (yr)	50.3 ± 19.5	46.8 ± 19.2	48.9 ± 20.9
Sex (male/female)	27/30	26/31	27/33
Body weight (kg)	70.4 ± 14.0	69.3 ± 11.8	63.2 ± 14.2
Morphine dose (mg)	7.0 ± 1.4	6.9 ± 1.2	—

TABLE 2

Local Anesthetics Used for Epidural Anesthesia, Operative Sites, and Frequency of Analgesia at Time of Injection of Morphine or Placebo

	Epidural morphine (n = 57)	Intramuscular morphine (n = 57)	Epidural saline (n = 60)
Mepivacaine 2% (%)	61	67	56
Bupivacaine 0.5% (%)	39	33	44
Operative site (n)			
Hip	15	18	18
Thigh	2	2	2
Knee	25	21	24
Calf and foot	15	15	16
Complete analgesia at time of injection of morphine or placebo (%)	93	95	98

TABLE 3

Postoperative Analgesia and Sleep for 24 Hours following Injection of Morphine or Placebo

	Epidural morphine (n = 57)	Intramuscular morphine (n = 57)	Epidural saline (n = 60)
No pain (%)	64*	27	16
Pain acceptable—no analgesics (%)	17*	12	20
Severe pain—analgesics required (%)	19*	61	64
Mean time (±SD) of onset of first severe pain following surgery (hr)	6.4 ± 3.7	4.5 ± 3.2	2.5 ± 4.8
Sleep during 1st postoperative night (%)			
Good	54*	36	38
Bad	14*	42	21

* $p < 0.05$ compared with data for intramuscular morphine (chi-square and *t*-test).

The additional need for analgesics and sedation was also significantly less following epidural morphine than following intramuscular morphine or epidural saline (Table 5). Patients asking for analgesics needed the same medications with the same frequency and dosage, irrespective of their groups.

Following epidural morphine, the mean pain level ratings were close to "no pain" (mean 1.1 to 1.3) during the course of the observation period and thus less than in either of the other groups, even though the latter received more analgesics and sedation (Fig 1).

More informative is the frequency of various pain levels during the period of observation. Following epidural morphine, no pain or mild pain was experienced more often than after intramuscular morphine or epidural saline (Fig 2). However, some patients complained of severe pain following epidural morphine.

In order to test the effect of age on the effect of epidural morphine, the patients were divided into two groups of those 50 years of age and less and those more than 50 years of age. The mean ages of both groups differed by 33 years. The efficacy of epidural morphine and the frequency and types of side effects were unrelated to age. The patients' weight and consequently the applied doses of epidural morphine were similar in both groups, as were responses to morphine or placebo.

The local anesthetic used for epidural anesthesia influenced the postoperative analgesia following epidural morphine. Following administration of bupivacaine, postoperative pain was less frequent, mean levels of pain over 24 hours were lower, sleep was better, analgesics were used less frequently, and postoperative general well-being was rated lower than following administration of mepivacaine.

TABLE 4

Postoperative Feeling of Well-being for First 24 Hours following Surgery

	Epidural morphine (n = 57)	Intramuscular morphine (n = 57)	Epidural saline (n = 60)
		%	
Good	82*	67	55
Moderate	14*	25	43
Poor	4*	8	2

* $p < 0.05$ compared with data for intramuscular morphine (chi-square test).

TABLE 5

Postoperative Use of Analgesics and Sedative

	Epidural morphine (n = 57)	Intramuscular morphine (n = 57)	Epidural saline (n = 60)
		%	
Analgesics (pentazocine, piritramide, or metamizol)	27*	63	66
Sedative (promethazine)	9*	23	36

* $p < 0.05$ compared with data for intramuscular morphine (chi-square test).

Side Effects

The most frequent side effect was disturbance of micturition. Following epidural morphine, spontaneous micturition was later, the urge to urinate—often discomforting—was felt more often, and the injection of carbachol as well as the catheterization of the urinary bladder were more common (Table 6). Older patients did not experience statistically greater problems in voiding than did younger ones.

Pruritus, without any signs of urticaria, either generalized or affecting only the trunk, the extremities, the face, or the genital region, was most common following epidural morphine. It was statistically less common following intramuscular morphine and never followed epidural saline (Table 6).

Nausea, vomiting, fatigue, and headache occurred equally frequently in the three groups of patients (Table 6).

Discussion

Results following epidural injection of saline indicate that after orthopedic surgery on the lower extremities, approximately one third of the patients experienced no pain or only mild pain after surgery. The intramuscular injection of morphine brought lit-

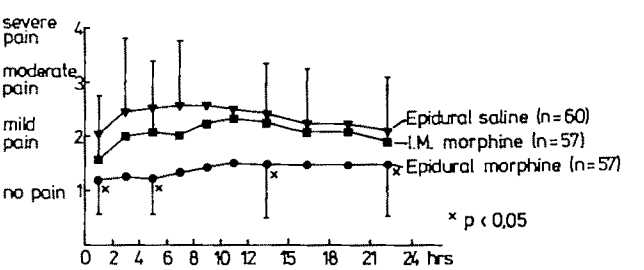


FIG 1. Mean (±SD) subjective ratings of pain for 24 hours following epidural morphine, intramuscular morphine, and epidural saline placebo, injected at end of orthopedic surgery; $p < 0.05$ between ratings for epidural and intramuscular morphine (t-test).

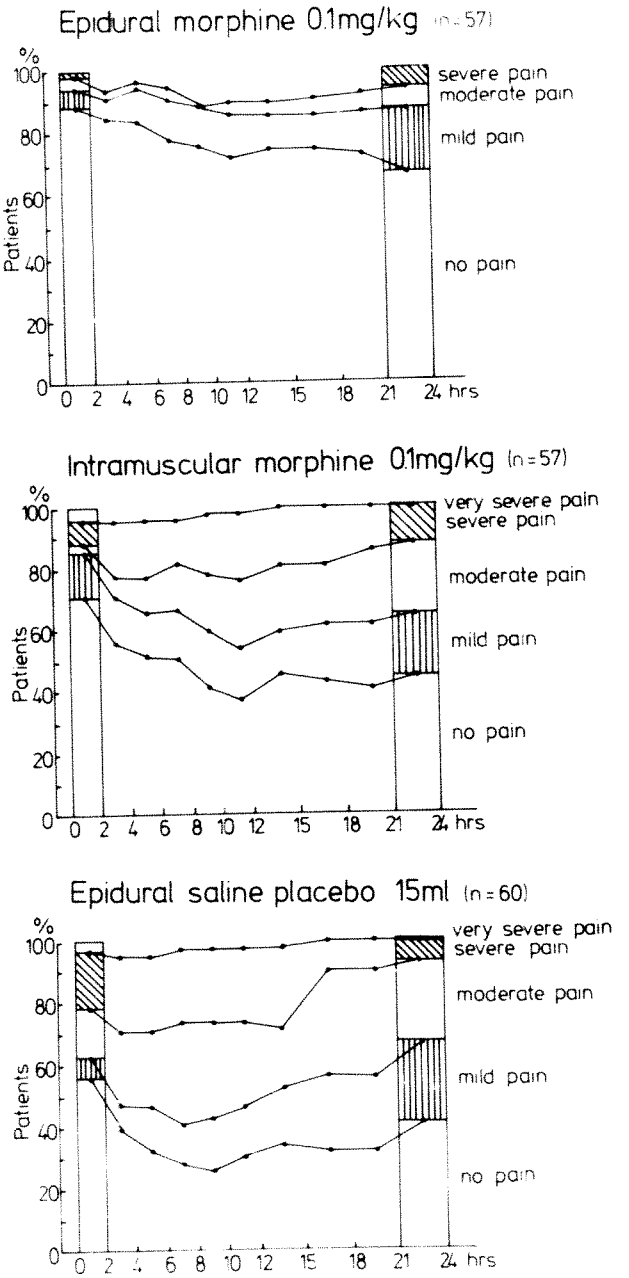


FIG 2. Frequencies of various pain levels for 24 hours following epidural morphine, intramuscular morphine, and epidural saline placebo injected at end of orthopedic surgery. Frequencies of pain following epidural and intramuscular morphine differ significantly ($p < 0.05$, chi-square test).

tle improvement of postoperative analgesia during the first 8 hours. Results with epidural morphine were superior to those in the other groups. It was, however, not successful in all patients, even though correct positioning of the catheter was evident as the same catheter provided adequate operative anesthesia. Our double-blind study confirms the positive results of

TABLE 6
Side Effects

	Epidural morphine (n = 57)	Intramuscular morphine (n = 57)	Epidural saline (n = 60)
Disturbances of micturition			
1st (±SD) spontaneous micturition* (hr after morphine)	8.7 ± 4.7*	6.9 ± 4.9	6.3 ± 5.7
Urge to urinate moderate (%)	51*	28	15
Urge to urinate severe (%)	20*	10	3
Intramuscular carbachol (%)	11*	2	8
Catheterization (%)	39*	20	12
Pruritus (%)	28*	4	0
Nausea (%)	7	2	12
Vomiting (%)	25	18	24
Fatigue (%)	53*	61	62
Headache (%)	9	4	4

* $p < 0.05$ compared with data for intramuscular morphine (chi-square and *t*-test).

previous uncontrolled studies of epidural morphine (1-4).

We chose the epidural dose of 0.1 mg/kg of body weight, because we found during a pilot study that using 2 to 4 mg of morphine resulted in unexpectedly extended latency times as well as several failures, which agrees with the results of other investigators (1, 3, 5-9). Also, Bromage et al (5) found that on the average 7.6 mg of morphine was needed for adequate analgesia following lower abdominal surgery and 10.3 mg of morphine following upper abdominal surgery. Most studies, however, have reported good analgesia for 24 hours with epidural doses less than 5 mg (2, 4, 7, 10-16).

Age had no influence on the analgesic effect of morphine. In patients of advanced age, in contrast to either the systemic administration of morphine or to the epidural injection of local anesthetics, analgesia cannot be achieved by a reduced dose of epidural morphine (5).

It is of clinical importance to note that more intensive analgesia by epidural morphine was associated with use of bupivacaine than with use of mepivacaine for epidural anesthesia. This phenomenon cannot be explained simply by the few hours' longer duration of bupivacaine analgesia. Bupivacaine should be preferred in combination with epidural morphine. We chose mepivacaine for this study in order to differentiate better the effects of epidural and intramuscular morphine in the postoperative period.

Approximately 20% of the patients experienced disturbances of micturition following the epidural saline placebo; twice as many had difficulty in voiding following intramuscular morphine (38%) and 4 times

as many (71%) following epidural morphine. Approximately 10% of the patients were catheterized following placebo, twice as many (20%) following intramuscular morphine and 4 times (40%) as many following epidural morphine. These problems occurred more frequently following 0.1 mg/kg of body weight than following 2 mg of epidural morphine, reported by Reiz et al. (7).

Pruritus was never observed following epidural saline, was rarely observed following intramuscular morphine, but was observed in approximately 25% of patients following epidural morphine. Localization of the pruritus, the lack of urticarial signs, and the higher frequency following epidural than following intramuscular morphine indicate the itching did not represent an allergic reaction. The morphine we administered did not contain any preservatives or additives (7).

The incidence of other side effects was not different in the three groups. Approximately 10% of patients complained of postoperative nausea, often only of short duration. Approximately 25% of patients vomited, often after the first sip of fluid, which was offered in the late evening of the operative day. Rarely did patients complain of headache.

Our study demonstrates that epidural morphine is more effective than equal doses of intramuscular morphine (7, 13, 17). Epidural morphine must, therefore, act on the spinal cord. The duration of analgesia following epidural morphine exceeds that following intramuscular morphine. Sympathetic block with ensuing circulatory changes does not occur (4, 16); orthostatic adaptation and mobilization are thus feasible earlier. However, all sensation is not blocked by epidural morphine; patients still notice pressure due to a cast or a dressing and perceive the danger of decubitus. There is no motor blockade and active mobilization is possible earlier. Following epidural morphine, awareness is heightened, cooperation is better, and respiratory depression and postoperative pneumonia are less frequent than after systemic administration of opiates (2, 5, 14, 16). The doses we administered, however, which are higher than those of most authors (2, 3, 5), do not provide postoperative analgesia in all patients. Side effects are more common than following intramuscular application. Respiratory depression may occur several hours following epidural morphine and requires careful and extensive monitoring (7–9, 14). Reduction of the epidural doses of morphine reduces the incidence of side effects, but also the adequacy of analgesia. For these reasons additional substances with more reliable analgesic effect and less side effects should be sought (18).

REFERENCES

1. Ebert J, Varner PD. The effective use of epidural morphine sulfate for postoperative orthopedic pain. Anesthesiology 1980;53:257–8.
2. Magora F, Olswang D, Eimerl D, et al. Observations on extradural morphine analgesia in various pain conditions. Br J Anaesth 1980;52:247–52.
3. Muller A, Straja A, Dupeyron JP, Franckhauser D, Dumeny E. Postoperative hypoalgesia by epidural morphine after abdominal surgery. In: Abstracts of the 7th World Congress of Anesthesiologists. Amsterdam: Excerpta Medica, 1980, Nr. 811.
4. Müller H, Börner U, Stoyanov M, Hempelmann G. Intraoperative peridurale Opiatanalgesie. Anaesthesist 1980;29:656–7.
5. Bromage PR, Camporesi E, Chestnut D. Epidural narcotics for postoperative analgesia. Anesth Analg 1980;59:473–80.
6. McClure JH, Chambers WA, Moore E, Scott DB. Epidural morphine for postoperative pain. Lancet 1980;1:975–6.
7. Reiz S, Ahlin J, Ahrenfeldt B, Andersson M, Andersson S. Epidural morphine for postoperative pain relief. Acta Anaesthesiol Scand 1981;25:111–4.
8. Weddel SJ, Ritter RR. Serum levels following epidural administration of morphine with relief of postsurgical pain. Anesthesiology 1981;54:210–4.
9. Scott DB, McClure J. Selective epidural analgesia. Lancet 1979;1:1410–1.
10. Asari H, Inoue K, Shibata T, Soga T. Segmental effect of morphine injected into the epidural space in man. Anesthesiology 1981;54:75–7.
11. Engquist A. Grundlagen der periduralen Opiat-Analgesie und klinische Erfahrungen. In: Zenz M, ed. Peridurale Opiat-Analgesie. Stuttgart: Fischer, 1981:1–17.
12. Graham JL, King R, McGaughey W. Postoperative pain relief using epidural morphine. Anaesthesia 1980;35:158–60.
13. Yu CM, Youngstrom PC, Cowan RI, Spagnuolo SET, Sutheimer C, Eastwood DW. Post-cesarean epidural morphine: double-blind study. Anesthesiology 1980;53:S216.
14. Piepenbrock S, Zenz M, Otten G. Peridurale Opiat-Analgesie in der postoperativen Phase. In: Zenz M, ed. Peridurale Opiat-Analgesie. Stuttgart: Fischer, 1981:47–67.
15. Zenz M, Piepenbrock S, Hüsch M, Otten G, Otten B. Peridurale Morphin-Analgesie. Anaesthesist 1981;30:28–30.
16. Zenz M, Piepenbrock S, Otten B, Otten G, Neuhaus R. Peridurale Morphin Analgesie. I. Postoperative Phase. Anaesthesist 1981;30:77–82.
17. Torda TA, Pybus DA, Liberman H, Clark M, Crawford M. Experimental comparison of extradural and im morphine. Br J Anaesth 1980;52:939–42.
18. De Castro J, Lecron L. Peridurale Opiat-Analgesie. Verschiedene Opiate. Komplikationen und Nebenwirkungen. In: Zenz M, ed. Peridurale Opiat-Analgesie. Stuttgart-New York: Fischer, 1981:103–28.

ANESTH ANALG
1982;61:241-6

Pharmacokinetics of *d*-Tubocurarine in Patients with Thermal Injury

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MARTYN, J.A.J., MATTEO, R. S., GREENBLATT, D. J., LEBOWITZ, P. W., AND SAVARESE, J. J.: Pharmacokinetics of *d*-tubocurarine in patients with thermal injury. Anesth Analg 1982;61:241-6.

d-Tubocurarine (dTc) requirements are increased following thermal injury. Significant increases in plasma binding only partially account for the altered requirement. To characterize the pharmacokinetic component of the increased requirement, the disposition of dTc was studied in eight patients with burns ranging from 15% to 80% of body surface area and compared with that in six nonburned surgical patients of comparable age and weight. Plasma levels of dTc were measured by radioimmunoassay at multiple times for 24 hours after a single bolus dose. Derived pharmacokinetic parameters were corrected for the predicted (not measured) fraction bound to plasma. The plasma disappearance curve of dTc was explained by linear sum of two or three exponential terms. The unbound central volume of distribution and renal excretion at 24 hours were significantly increased in burned patients (0.11 ± 0.03 L/kg vs 0.057 ± 0.015 L/kg, $p < 0.05$, 57% ± 7% vs 40% ± 11%, $p < 0.05$, respectively). On the other hand, comparable elimination half-lives (6.5 ± 1.8 hr vs 6.2 ± 1.3 hr, $p > 0.05$), unbound volume of distribution (0.86 ± 0.2 L/kg vs 0.96 ± 0.5 L/kg, $p > 0.05$), and intrinsic clearances (1.62 ± 0.6 ml/kg/min vs 1.56 ± 0.4 ml/kg/min, $p > 0.05$) were present in burned patients and control patients, respectively. Thus, altered kinetics contributes little to the increased doses required. Similar clearances and elimination half-lives in both groups suggest that loss of dTc through burned tissue is minimal.

Key Words: PHARMACOKINETICS: *d*-tubocurarine; COMPLICATIONS: burns; NEUROMUSCULAR RELAXANTS: *d*-tubocurarine.

RECENT studies (1) indicate that the dose and plasma concentrations of *d*-tubocurarine (dTc) required to attain a given degree of twitch depression are considerably elevated following burns. Compared with nonburned patients, there was a 3-fold increase in the intravenous dose and a 5-fold increase in the plasma concentration required to produce a specified level of neuromuscular blockade. Despite significant augmentation of the plasma binding of dTc following burn injury, the altered binding only partially explains the hyposensitivity (2). There is indirect evidence to suggest changes at the neuromuscular junction which may account for the altered response following burns (1-4). However, the pharmacokinetic component of the altered dose requirement is unknown. To date, pharmacokinetic analyses in burned patients are few in number. Glew, Moellering, and Burke (5) documented the exudation of gentamycin through burn wounds, probably explaining the need for more frequent doses. Alternately, rapid urinary excretion due to enhanced glomerular filtration has been suggested

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Supported in part by grants from the Shriners Burns Institute, United States Public Health Service grants #GM 21700, 09069, and MH 34223.

Received from the Department of Anesthesia, Harvard Medical School, Anesthesia Services of the Massachusetts General Hospital, Boston, Massachusetts; Department of Anesthesiology, College of Physicians & Surgeons, Columbia University and Anesthesia Services of Presbyterian Hospital, New York, New York; and Division of Clinical Pharmacology, Departments of Psychiatry and Medicine, Tufts-New England Medical Center, Boston, Massachusetts. Accepted for publication November 10, 1981. Presented in part at the 55th Congress of the International Anesthesia Research Society March 9-12, 1981, Atlanta, Georgia.

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as the reason for the low serum tobramycin levels in these patients (6). Another possible mechanism for the increased dose requirement included an altered distribution volume (7). Thus, the present study of pharmacokinetics and disposition of dTc following burn trauma was undertaken to elucidate the pharmacokinetic component of the altered clinical response.

Methods and Materials

Eight patients with greater than 15% body surface area burns were studied during surgery at varying times following burn injury and were compared with six general surgical patients of comparable age and weight who had not sustained a burn. Informed consent was obtained and the study was approved by the institutional review board for human studies. The characteristics of the burned patients and control patients are summarized in Table 1. Both control and burned patients had normal renal, hepatic, and cardiac function as evidenced by normal laboratory values of blood urea nitrogen (BUN) and creatinine, serum bilirubin, serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) and normal atrial filling pressures, systemic blood pressure, and electrocardiogram (ECG). Five burned patients had cardiac indices measured within 24 hours of the anesthetic and were in excess of 4 L/min/m^2.

All patients were premedicated with morphine (0.1 mg/kg IM) and/or diazepam (0.1 mg/kg by mouth). Anesthesia was induced with thiopental (4 to 6 mg/kg) and maintained with nitrous oxide/oxygen. Incremental doses of morphine or fentanyl were administered based on pulse, blood pressure, tearing, and pupillary size. Ventilation was controlled to maintain Pa_{O_2} within normal limits. Esophageal temperature was maintained between 34.5 and 37°C. All patients were given an intravenous infusion of lactated Ringer's solution, 500 to 800 ml, before induction of anesthesia. Throughout anesthesia and surgery, maintenance intravenous fluids consisted of lactated Ringer's solution or 5% dextrose in water at a rate of 4 to 6 ml/hr. Blood loss was estimated by weighing of sponges and/or serial estimate of the hematocrit. When indicated, blood loss was replaced volume-for-volume to maintain an hematocrit greater than 30%, which varied between one and four units. Duration of anesthesia was between 3 and 5 hours.

Following induction of anesthesia, a single bolus dose of 0.5 mg/kg of dTc (as the hydrochloride salt)

TABLE 1
Clinical Characteristics of Patients

Patient no.	Age	Sex	Body weight	Total protein	Burn size (% body surface area)	Postburn day of study
	yr		*kg*	*g%*		
Burn patients						
B-1	23	M	64	4.9	15	8
B-2	39	M	74	6.2	75	11
B-3	19	M	74	5.3	25	7
B-4	11	M	48	4.8	80	19
B-5	37	M	74	5.5	80	13
B-6	24	M	70	5.5	42	8
B-7	50	M	89	5.5	56	5
B-8	56	M	82	5.5	15	1
Mean	32.4		71.6	5.4	49	9
±SD	±15.7		±12.0	±0.3*	±15	±5
Control patients						
C-1	36	F	66	7.7		
C-2	35	M	80	6.6		
C-3	24	M	70	5.5		
C-4	22	M	55	6.5		
C-5	49	M	60	5.8		
C-6	66	M	49	—		
Mean	38.7		62.2	6.4		
±SD	±16.5		±11.0	±0.9		

* $p < 0.05$.

was administered intravenously. Blood samples were obtained from an arterial or a separate central venous catheter 1, 3, 5, 10, 15, 30, and 45 minutes and 1, 2, 3, 4, 6, 9, 12, 15, 18, 21, and 24 hours following injection. The plasma was separated and frozen until analyzed for dTc concentration. In five burned patients and in five control patients the 24-hour urinary excretion of dTc was determined based on urine collection from an indwelling Foley catheter. Plasma and urine dTc concentrations were determined by the radioimmunoassay of Horowitz and Spector (8), with a sensitivity limit of 1 ng/ml in serum. The coefficient of variation for identical samples does not exceed 5%.

Plasma dTc concentrations were analyzed by iterative nonlinear least-squares regression techniques described previously (9, 10). Data points were fitted to a linear sum of two or three exponential terms. The choice between a two- or three-exponential equation as function of best fit was based upon the sum of squares of weighted residual errors, and on the scatter of actual data points about the fitted function.

Coefficients and exponents from the fitted functions were used to calculate the following kinetic variables: initial distribution half-life ($t_{1/2\alpha}$), elimination half-life ($t_{1/2\beta}$) corresponding to the terminal phase of the disappearance curve (the smallest exponent), volume of central compartment or initial volume of distribution (V_i), total volume of distribution using the area method (V_d), and total clearance (Cl_{tot}). At the time this study was performed, the possible role of individual differences in plasma protein binding on dTc pharmacokinetic properties was not anticipated. Therefore, the blood sample volume obtained for the kinetic study was small, and insufficient volume remained after measurement of total dTc concentrations for quantitation of plasma protein binding. Therefore, the extent of dTc binding was estimated based upon previous studies in our laboratories. In normal subjects, there is little individual variation in the amount of dTc bound to plasma (2, 11); binding for the nonburned control patients in the present study therefore was estimated as the mean value for nonburned individuals. Following thermal injury to skin, there is an increased binding of dTc to plasma protein. Our studies, published and unpublished, have established that dTc binding in burned patients can be predicted based on the time elapsed since thermal injury. For the present study, dTc binding in burned patients was estimated based upon this relationship.

Pharmacokinetic parameters for total dTc were then corrected for protein binding, yielding corresponding values of unbound V_i ($V_{i,\,unb}$), unbound V_d($V_{d,\,unb}$), and unbound (intrinsic) clearance (Cl_{int}). Student's unpaired *t*-test was used to establish differences between burned and unburned groups.

Results

Disappearance of dTc from plasma in the majority of patients was described by a linear sum of three exponential terms, consistent with a three-compartment pharmacokinetic model (Figure). The individual pharmacokinetic parameters for each patient together with the mean (±SD) for each group are shown in Table 2. Because of increased affinity of dTc to plasma protein following burns, V_d and Cl_{tot} were smaller in burn patients compared with control patients; however, when corrected for binding $V_{d,\,unb}$ and Cl_{int} were not significantly different. V_i was similar in both groups, which when corrected for binding, was significantly greater in burned patients than in control patients. The urinary excretion as a fraction of the total dose, although not different at 6 hours, was significantly elevated at 24 hours in burned patients. The increased fraction of the dose appearing in urine in burned patients was not sufficient to cause a difference in the intrinsic clearance in the two groups. The fact that elimination half-lives and intrinsic clearances are similar in both groups suggests that signif-

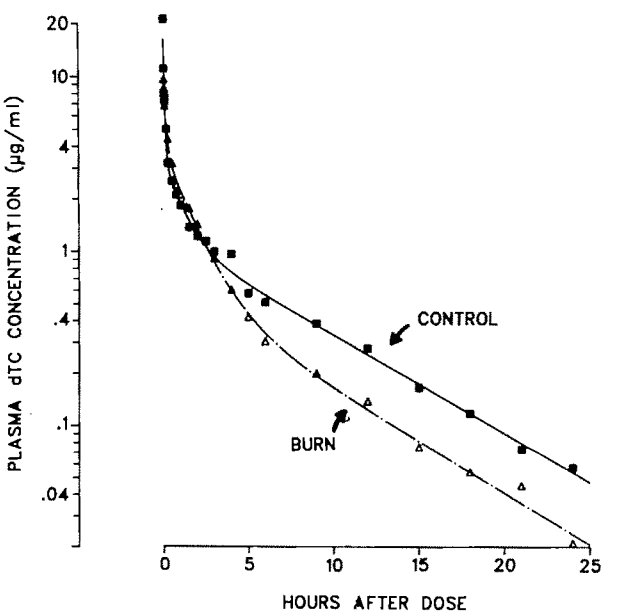


FIGURE. Total plasma (*d*-tubocurarine) dTc concentrations in representative burned and control patients. Lines represent pharmacokinetic functions determined by nonlinear least-square regression analysis.

TABLE 2
Pharmacokinetic Variables*

Patient no.	$t_{1/2\alpha}$	$t_{1/2\beta}$	V_i	V_d	Cl_{tot}	Calculated % bound	$V_{i,unb}$	$V_{d,unb}$	Cl_{int}	Urinary excretion at: 6 hr	Urinary excretion at: 24 hr
	min	*hr*	*L/kg*		*ml/kg/min*		*L/kg*		*ml/kg/min*	%	
Burn patients											
B-1	5.3	5.1	0.050	0.360	0.822	69	0.161	1.16	2.65	38.2	54.6
B-2	2.1	9.7	0.030	0.292	0.349	71	0.103	1.01	1.20		
B-3	3.3	7.4	0.036	0.235	0.367	67	0.109	0.71	1.11	32.9	55.1
B-4	2.5	4.4	0.033	0.257	0.668	73	0.122	0.95	2.47	35.7	69.8
B-5	1.0	6.8	0.024	0.216	0.366	72	0.086	0.77	1.31	34.9	51.2
B-6		7.9		0.303	0.445	69		0.98	1.44		
B-7	2.2	5.9	0.024	0.271	0.533	62	0.063	0.71	1.40		
B-8	10.9	4.6	0.063	0.276	0.689	51	0.129	0.56	1.41	46.9	56.1
Mean	3.9	6.5	0.037	0.276	0.530	66.8	0.11	0.86	1.62	37.7	57.4
±SD	±3.4	±1.8	±0.014	±0.044†	±0.178†		±0.03†	±0.20	±0.59	±5.5	±7.2†
Control patients											
C-1		5.7		0.52	1.047	50		1.80	2.09	57.7	
C-2	2.3	5.4	0.016	0.234	0.503	50	0.032	0.47	1.01	21.2	40.3
C-3	3.1	7.6	0.032	0.564	0.854	50	0.064	1.13	1.71	23.2	34.2
C-4	9.0	5.1	0.03	0.410	0.936	50	0.060	0.82	1.87	22.8	34.9
C-5	2.8	5.3	0.028	0.278	0.603	50	0.056	0.56	1.21	31.6	58.4
C-6	3.8	8.0	0.036	0.489	0.704	50	0.072	0.98	1.41	9.8	33.4
Mean	4.2	6.2	0.028	0.416	0.774	50	0.057	0.96	1.56	27.7	40.2
±SD	±2.8	±1.3	±0.008	±0.134	±0.207		±0.015	±0.48	±0.41	±16.3	±10.5

* Abbreviations used are: $t_{1/2\alpha}$, distribution half-live; $t_{1/2\beta}$, elimination half-live, V_i, initial volume of distribution; V_d, total volume of distribution; Cl_{tot}, total clearance, $V_{i,unb}$, unbound V_i; $V_{d,unb}$, unbound V_d; Cl_{int}, unbound (intrinsic) clearance.

† $p < 0.05$ for control patients vs burned patients.

icant amounts of dTc were not lost through burn wound.

Discussion

The present study confirms previous reports (11–15) that the disappearance of dTc from plasma in the majority of patients is consistent with the sum of three exponential terms. Our findings indicate that the kinetics of dTc in burned and nonburned patients are different in that the central volume of distribution and renal excretion at 24 hours are significantly higher in the former. However, this observed alteration in pharmacokinetics can contribute only minimally to the altered dose requirement as the unbound total volume of distribution and renal excretion at 6 hours are not significantly different. Although exudation through burn wound is a factor in increased gentamycin requirements (5), comparable plasma half-lives and intrinsic clearances in the two groups imply minimal loss of dTc through burn wound.

The dTc kinetics based upon total (free plus bound) plasma concentrations suggest that burned patients have smaller values of V_d and Cl_{tot}. However, recent studies by Leibel et al (2) indicate that following thermal injury there is a 1.7-fold increase in plasma binding of dTc. Despite a decrease in total protein, the percentage of dTc which is bound increases with time, peaks at 2 weeks, and then plateaus and remains elevated even 90 days later. In nonburned subjects, there is little variation in the amount of dTc bound to plasma protein (2, 9). Almost all analytic techniques measure total plasma concentrations and hence prior studies on dTc pharmacokinetics did not take into consideration the effects of binding. As long as binding does not differ greatly between individuals, pharmacokinetics analysis based on total plasma concentrations remain meaningful. However, when there is extensive binding by plasma, as in the case of burns, the interpretation of many pharmacokinetic parameters may change (16). Therefore, it was more logical and meaningful to calculate the pharmacokinetic parameters of free drug that is available for equilibration with extravascular space.

Unfortunately, the need for binding measurements was not anticipated when this study was done, and such measurements were not available. This is a

TABLE 3
Comparison of Pharmacokinetic Variables*

	Stanski (19) (mean ± SD)	Matteo (12) (mean ± SE)	Meijer (11) (mean ± SE)	Martyn† (mean ± SD)	Matteo (12) (mean ± SE)
Duration of sampling (hr)	4	6	12	24	48
$t_{1/2}\alpha$ (min)	6.2 ± 3.7	—	1.7 ± 0.4	4.2 ± 2.8	—
$t_{1/2}\beta$ (hr)	2.0 ± 1.1	2.7 ± 0.2	5.8 ± 2.9	6.2 ± 1.3	40.1 ± 2.7
V_i (L/kg)	0.099 ± 0.027	0.039 ± 0.003	0.047 ± 0.002	0.028 ± 0.008	0.04 ± 0.004
V_d (L/kg)	0.297 ± 0.105	0.420 ± 0.02	0.387 ± 0.054	0.416 ± 0.134	3.36 ± 0.33
Cl_{tot} (ml/kg/min)	2.25 ± 0.70	1.8 ± 0.1	0.93 ± 0.2‡	0.774 ± 0.207	1 ± 0.1
Urinary excretion at 24 hr (% of dose)	—	—	47.6 ± 2.1	40.2 ± 10.5	44 ± 3

* Abbreviations are defined in footnote to Table 2.
† Nonburned subjects only (present study).
‡ Calculated on the assumed weight of 60 kg.

limitation of the study. However, we have previously studied dTc binding in healthy individuals and burned patients (2) and values of V_i, V_d, and Cl_{tot} were corrected for expected values of protein binding, yielding values of unbound central volume of distribution ($V_{i,unb}$), unbound total volume of distribution ($V_{d,unb}$), and intrinsic clearance (Cl_{int}). After corrections for binding, $V_{d,unb}$ and Cl_{int} were not significantly different, although $V_{i,unb}$ was almost twice that in nonburned control patients. This is consistent with the increased volume of extracellular water found in burned patients (17, 18). Nonetheless, the effects of the larger $V_{i,unb}$ on dosage requirements should be minimal. As in other studies (11, 19), we found the dTc distribution phase proceeded rapidly with an apparent half-life ($t_{1/2}\alpha$) of only a few minutes.

Comparison of dTc kinetics in the present investigation with those of previous studies demonstrates how duration of sampling can influence the interpretation of a single-dose pharmacokinetic study (20). Stanski et al (19) measured plasma dTc concentrations during nitrous oxide/narcotic anesthesia for no more than 4 hours. Thus, kinetic analysis yielded shorter $t_{1/2}\beta$ and smaller V_d than our 24-hour study (Table 3) (20). On the other hand, more recent studies of Meijer (11) and Matteo and co-workers (12) used 12- and 48-hour sampling times. As anticipated, our values for $t_{1/2}\beta$ and V_d for control patients lie between those reported in the 12- and 48-hour studies (Table 3).

Apparently 50% of a dose of dTc administered to humans is excreted in 24 hours by the renal route (11, 12) via glomerular filtration (12, 21). Our findings in nonburned patients are consistent with this. As only the unbound drug is available for filtration (16), one might predict decreased renal excretion of dTc in burned patients. However, the burned patients at 24 hours had a significantly higher renal elimination than nonburned patients despite increasing binding. Tobramycin excretion also increases following burns because of increased glomerular filtration related to higher cardiac output (6). In our burned patients, the enhanced glomerular filtration probably more than compensated for the increased binding. In any case, the increased fraction of the dose appearing in urine was not sufficient to cause a difference in intrinsic clearance, as renal clearance of intact dTc accounts for only part of the total drug clearance from the body. Nonetheless, similar urinary excretions at 6 hours in the two groups indicate that increased urinary excretion is not likely to play a major role clinically in the increased dose requirement.

Thus, it appears that the increased dTc requirement following thermal injury is not related to an increase in volume of distribution nor is it due to leakage through burn wound as shown for gentamycin. Inasmuch as urinary excretion of dTc differs significantly in burned patients only 24 hours after administration of dTc, enhanced renal excretion secondary to increased glomerular filtration rate cannot explain the heightened dTc requirement in these patients. Likewise, increased plasma binding of dTc only partially provides an explanation. Consequently, this study complements previous speculations (1–4), that more fundamental changes at target tissues, namely an increase in the number of acetylcholine receptors at the neuromuscular junction or an altered affinity for dTc by these receptors, may be responsible for the elevated demand for dTc.

ACKNOWLEDGMENTS

We express our thanks to Aleta Radoš for secretarial help. We are grateful to Dr. Darrell Abernethy, Ann Locniskar, and Jaime Diaz for their assistance.

REFERENCES

1. Martyn JAJ, Szyfelbein SK, Ali HH, Matteo RS, Savarese JJ. Increased d-tubocurarine requirement following major thermal injury. Anesthesiology 1980;52:352–5.
2. Leibel WS, Martyn JAJ, Szyfelbein SK, Miller KW. Elevated plasma binding cannot account for the burn related d-tubocurarine hyposensitivity. Anesthesiology 1981;54:378–82.
3. Gronert GA, Theye RA. Pathophysiology of succinylcholine hyperkalemia. Anesthesiology 1975;43:89–99.
4. Gronert GA. A possible mechanism for succinylcholine induced hyperkalemia. Anesthesiology 1980;53:356.
5. Glew RH, Moellering RC, Burke JF. Gentamycin dosage in children with extensive burns. J Trauma 1976;16:819–23.
6. Loirat P, Rohan J, Bailet A, Beaufils F, David R, Chapman A. Increased glomerular filtration rate in patients with major burns and its effect on pharmacokinetics of tobramycin. N Engl J Med 1978:299:915–9.
7. Flandrois JP, Marichy J, Ceyrat J. Pharmacocinetique de l'amikacine chez le brule (resultas preliminaires). Nouv Presse Med 1979;8:3501–2.
8. Horowitz PE, Spector S. Determination of serum d-tubocurarine concentration by radioimmunoassay. J Pharmacol Exp Ther 1973;185:94–100.
9. Greenblatt DJ, Allen MD, Harmatz JS, Shader RI. Diazepam disposition determinants. Clin Pharmacol Ther 1980;27:301–12.
10. Marquardt DW. An algorithm for least squares estimation of nonlinear parameters. J Soc Ind Appl Math 1963;11:431–41.
11. Meijer DKF, Weitering JG, Vermeer GA, Scaf AHJ. Comparative pharmacokinetics of d-tubocurarine and metocurine in man. Anesthesiology 1979;51:402–7.
12. Matteo RS, Nishitateno K, Pua EK, Spector S. Pharmacokinetics of d-tubocurarine in man: effect of osmotic diuretic on urinary excretion. Anesthesiology 1980;52:335–8.
13. Gibaldi M, Levy G, Hayton W. Kinetics of the elimination and neuromuscular effect of d-tubocurarine in man. Anesthesiology 1972;36:213–8.
14. Wingard LB, Cook DR. Pharmacodynamics of tubocurarine in humans. Br J Anaesth 1976;48:839–45.
15. Miller RD, Matteo RS, Bennett LZ, Sohn YJ. Pharmacokinetics of d-tubocurarine in man with and without renal failure. J Pharmacol Exp Ther 1979;202:1–7.
16. Greenblatt DJ, Koch-Weser J. Clinical pharmacokinetics. N Engl J Med 1975;702–5; 964–76.
17. Martyn JAJ, Burke JF. Is there a selective increase in pulmonary capillary permeability following cutaneous burns? Chest 1979;76:374–5.
18. Martyn JAJ, Snider MT, Szyfelbein SK, Burke JF, Laver MB. Right ventricular dysfunction in acute thermal injury. Ann Surg 1980;191:330–5.
19. Stanski DR, Ham J, Miller RD, Sheiner LB. Pharmacokinetics and pharmacodynamics of d-tubocurarine during nitrous oxide-narcotic and halothane anesthesia. Anesthesiology 1979;51: 235–41.
20. Fell PJ, Pharmacokinetics: uses and abuses. Eur J Clin Pharmacol 1975;8:241–8.
21. Cohen EN. Uptake, distribution and elimination of muscle relaxants. In: Scurr C, Feldman SA, eds. Scientific foundations of anesthesia. London: William Heineman, 1974:454–60.

Cardiac Arrhythmias in Patients with Acute Cerebrovascular Accidents

To assess the incidence and severity of cardiac arrhythmias in the acute period following a cerebrovascular accident (CVA), 30 patients with a CVA underwent 24 hours of continuous ECG recording in a neurologic intensive care unit. Twenty patients electively admitted for cataract surgery served as a control group and also had continuous ECG recording. Of 30 CVA patients 15 (50%) had serious ventricular ectopy, compared with only three (15%) of the 20 control subjects. Among the patients with CVA, two had ventricular tachycardia, two had complete atrioventricular block, and two had asystole, all occurring in CVAs involving the anterior circulation. None of the control subjects experienced these arrhythmias. Cardiac arrhythmias are common in patients with acute CVAs, especially those involving the anterior circulation. Dynamic ECG recordings may detect such arrhythmias and provide data for therapeutic consideration. *(Mikolich JR, Jacobs WC, Fletcher GF. Cardiac arrhythmias in patients with acute cerebrovascular accidents. JAMA 1981;246:1314–7)*

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1982;61:247-51

Effects of Protamine Sulfate on Myocardial Oxygen Supply and Demand in Patients following Cardiopulmonary Bypass

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SETHNA, D., MOFFITT, E., GRAY, R. J., BUSSELL, J., RAYMOND, M., CONKLIN, C., AND MATLOFF, J. M.: Effects of protamine sulfate on myocardial oxygen supply and demand in patients following cardiopulmonary bypass. Anesth Analg 1982;61:247-51

The effect of protamine sulfate on myocardial oxygen supply and demand was studied under clinical conditions in nine patients following cardiopulmonary bypass. Before surgery, the patients had severe coronary artery disease with good ventricular function. The patients required no vasoactive drugs, but only blood volume adjustments when weaned off bypass, and were hemodynamically stable at the time of study. The protamine dose of 196 mg (2.5 mg/kg) was infused over 4 ± 1 minutes. Although modest variation in hemodynamic function occurred in individual patients after administration of protamine, there were no significant hemodynamic alterations for the group. No significant alteration in global myocardial metabolism was observed. Protamine caused a small decrease in measured coronary blood flow, resulting in a corresponding reduction in calculated myocardial oxygen consumption as coronary sinus oxygen content remained unaltered. Myocardial lactate extraction showed no significant alteration. It is concluded that protamine sulfate, given at rapid infusion rates in hemodynamically stable patients, is not associated with an adverse alteration in hemodynamics or global myocardial metabolism.

Key Words: ANESTHESIA: cardiovascular; BLOOD: coagulation, heparin; HEART: metabolism.

PROTAMINE SULFATE has been used in the reversal of the anticoagulant effect of heparin since the advent of cardiopulmonary bypass (1). The hemodynamic effects of protamine, described in detail in intact animals (2-7), in general showed that the drug caused a significant hypotension. Limited studies in man (8, 9) indicate that the drug exerts much less effect on systemic hemodynamics in therapeutic doses. Consideration of the clinical use of the drug in cardiac patients must include an appreciation of the effects of the drug on myocardial oxygen supply and demand, as protamine may impose an undesirable metabolic cost on the myocardium simultaneous with its clinical effect. An evaluation of the myocardial metabolic cost of protamine following cardiopulmonary bypass has not been described. Hence, the goal of this study was to examine the acute effects of protamine sulfate on myocardial oxygen consumption and myocardial lactate extraction, in adult patients who had undergone cardiopulmonary bypass for coronary artery bypass grafting (CABG), relating the findings to concurrent changes in hemodynamics.

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Methods and Materials

This investigation was performed during a larger project which included 30 patients undergoing coronary artery bypass grafting who were studied before induction of anesthesia through surgery and for 24 hours afterwards. The protocol was approved by the Human Subjects Committee of our institution. In-

formed consent was obtained from all patients. Before surgery, all patients had severe coronary artery disease, with preserved myocardial function as evaluated by angiographic ejection fraction. All patients were in normal sinus rhythm. Excluded from our study were patients with clinical diabetes mellitus, valvular heart disease, moderate arterial hypertension (diastolic blood pressure greater than 105 mm Hg), significant pulmonary disease, left ventricular end-diastolic pressure (LVEDP) greater than 20 mm Hg at rest or greater than 15 mm Hg after nitroglycerin, and patients with myocardial infarctions within 2 weeks. Patients with angiographically minimal ischemic mitral regurgitation were included. Nine patients who required no vasoactive drugs but only blood volume adjustments when weaned off bypass were the subjects of the present study. Their clinical characteristics are shown in Table 1. Anatomically, each patient was judged to be completely revascularized by the surgeon, as all vessels with greater than 50% obstruction were bypassed. None of the patients developed a perioperative myocardial infarction as assessed by serial electrocardiography and serum enzyme determinations.

Before anesthesia the following catheters were introduced in each patient: (*a*) an 18-gauge cannula into the radial artery; (*b*) a thermodilution triple-lumen catheter (Edwards) by the Seldinger technique through the right internal jugular vein into the pulmonary artery; and (*c*) a coronary sinus catheter (Wilton-Webster Laboratories, Altadena, CA) through the same internal jugular vein into the coronary sinus by fluoroscopy, so that the external thermistor was 10 to 20 mm inside the coronary sinus. The vein grafts were performed during whole body perfusion with core cooling to 20 to 25 C. Crystalloid potassium or blood cardioplegia and topical myocardial hypothermia (4 C) were utilized. Five of the patients (patients 3 to 7, Table 2) were anesthetized with halothane and oxygen, and the rest received morphine (1 mg/kg) and oxygen. Inductions with halothane began with up to 2.5% halothane inspired in oxygen, and thereafter anesthesia was maintained with 0.5% to 1% halothane and oxygen. The study was done at the usual time of giving protamine postpump, after optimum increase in blood volume by arterial transfusion of perfusate.

After control measurements, protamine sulfate (2.5 mg/kg; mean dose 196 mg) was infused over 3 to 6 minutes (Table 2). Conditions during the study were maintained as close to a steady state as possible. Blood volume was not adjusted. Surgical manipulation of the heart was deferred during all measurements. No vasoactive drug was administered during the study.

TABLE 1
Clinical Characteristics of Study Patients

No. (male/female)	7/2
Age* (yr)	59 ± 8
Weight* (kg)	78 ± 11
Coronary Friesinger score* (10)	11 ± 3
Preoperative ejection fraction*	70 ± 13
No. of grafts (range)	2–5
Ischemic time* (min)	73 ± 19
Pump time* (min)	122 ± 23
Lowest body temperature on cardiopulmonary bypass* (C)	21 ± 2
Heparin dose on cardiopulmonary bypass (mg)	
Mean	279
Range	210–375
Protamine dose (mg)	
Mean	196
Range	120–275
Time of protamine infusion* (min)	4 ± 1

* Mean ± SD.

Coronary blood flow was measured by the thermodilution technique as described by Ganz et al (11). Arterial and coronary sinus blood samples were obtained simultaneously for determination of lactate and oxygen concentrations. Lactate samples were analyzed in duplicate by modification of the Marbach method (12). Blood samples were analyzed immediately for hemoglobin and oxygen saturation (IL Co-oximeter, model 282). Systemic and pulmonary arterial, pulmonary capillary wedge, and right atrial pressures were measured and recorded on paper using a six-channel chart recorder (VR-6 Electronics for Medicine). Cardiac output was measured in duplicate by thermodilution. Arterial blood pressure, electrocardiogram (ECG) lead II, and the patient's clinical condition were continually monitored. Measurements were repeated 10 minutes after completion of the protamine infusion.

Hemodynamic indices were calculated from measured variables according to standard formulas (13). Metabolic indices were calculated as follows:

$$\text{lactate extraction ratio} = \frac{\text{ART (lactate)} - \text{CS (lactate)}}{\text{ART (lactate)}}$$

where ART (lactate) is the arterial lactate concentration (meq/L) and CS (lactate) is the coronary sinus lactate concentration (meq/L).

$$MV_{O_2} = CBF \times (\text{ART \{oxygen\}} - \text{CS \{oxygen\}})$$

where MV_{O_2} is oxygen consumption of the myocardium drained by the coronary sinus (predominantly the left ventricular myocardium) and CBF is coronary sinus blood flow.

TABLE 2
Hemodynamic Responses to Protamine in Patients following Cardiopulmonary Bypass*

Patient no.	Protamine dose	Infusion time	Intervention	HR	MAP	PA	PCWP	SVR	CI
	mg	*min*		*beats/min*		*mm Hg*		*dyne·sec·cm^{-5}*	*L/min/m^2*
1	150	3	Before	81	69	16	15	1348	1.99
			After	87	69	18	15	1821	1.50
2	200	4	Before	87	69	10	8	1062	2.67
			After	85	59	11	8	819	2.90
3	275	5	Before	75	93	14	10	1891	1.91
			After	74	80	14	12	1664	1.82
4	176	6	Before	73	85	18	16	1128	2.82
			After	64	84	19	15	1411	2.20
5	255	4	Before	87	86	19	19	1387	2.44
			After	84	90	15	13	1336	2.59
6	120	3	Before	79	81	22	22	1423	2.28
			After	72	69	14	10	1605	1.85
7	200	3	Before	85	94	21	14	1201	2.60
			After	89	98	21	15	2496	1.34
8	200	3	Before	65	92	18	13	1842	1.67
			After	69	98	16	11	1857	1.79
9	190	5	Before	83	85	16	12	1657	1.88
			After	77	93	16	14	1368	2.59
Mean	196	4	Before	79 ± 7	84 ± 9	17 ± 4	14 ± 4	1438 ± 300	2.25 ± 0.4
± SD	48	1	After	78 ± 9	82 ± 14	16 ± 3	13 ± 3	1597 ± 460	2.06 ± 0.5
Significance				NS	NS	NS	NS	NS	NS

* Abbreviations used are: HR, heart rate; MAP, systemic mean arterial pressure; PA, mean pulmonary arterial pressure; PCWP, mean pulmonary capillary wedge pressure; SVR, systemic vascular resistance; CI, cardiac index; NS, not significant.

Statistical evaluation was done using the Wilcoxon paired test, comparing measurements before and after administration of protamine in each patient. Results are expressed as means ± SD. The Wilcoxon test was used instead of the paired *t*-test because of the relatively small sample sizes and in order to avoid the assumption of normality in the two populations that is made by the *t*-test. It is important to note that when the assumptions of the *t*-test are not met, the Wilcoxon test may in fact be superior to the *t*-test (14).

Results

Hemodynamic data before and 10 minutes after the protamine infusion for each patient are listed in Table 2. Before infusion of protamine, mean cardiac index was 2.25 L/min/m^2, with pulmonary capillary pressure of 14 mm Hg and mean arterial pressure of 84 mm Hg. After infusion of protamine there were no significant alterations in hemodynamic variables for the group. However, modest variation in hemodynamic function occurred in individual patients. Systemic vascular resistance increased in four patients, decreased in three patients, and remained unchanged in two patients.

The myocardial metabolic results for each patient are shown in Table 3. Protamine increased the calculated coronary vascular resistance in six patients, giving a mean increase of 26% for the entire group (0.77 ± 0.58 to 0.97 ± 0.57 mm Hg/ml/min; $p < 0.05$). This was accompanied by a 21% reduction in mean coronary blood flow (128 ± 55 to 101 ± 54 ml/min), resulting in a 15% decrease in the calculated mean myocardial oxygen consumption for all nine patients (7.1 ± 2.4 to 6.0 ± 2.1 ml/min), neither of which reached statistical significance. The mean coronary sinus oxygen content remained unchanged (6.1 ± 0.9 to 6.0 ± 1.1 ml of O_2 per deciliter). Although variations in myocardial lactate extraction were found between patients, alterations in mean myocardial lactate extraction for the entire group were not significant (11.4% ± 21% to 9.7% ± 10%). Because neither heart rate nor blood pressure changed, the rate-pressure product did not change (9205 ± 1146 to 8706 ± 1421).

It is evident from the data that no adverse hemodynamic reaction took place. Continued ECG monitoring revealed no alterations in cardiac rhythm or in ST segments or T wave patterns.

Discussion

Although the cardiovascular effects of protamine sulfate have been described in man (8, 9), the myocardial metabolic cost imposed by the drug is un-

TABLE 3

Myocardial Metabolic Responses to Protamine in Patients following Cardiopulmonary Bypass*

Patient no.	Intervention	CBF	CVR	$CS\text{-}O_2$ content	MV_{O_2}	MLE	RPP
		ml/min	*mm Hg/ml/min*	*ml O_2/dl*	*ml/min*	%	*units*
1	Before	71	0.85	6.3	4.3	−22	7,371
	After	68	0.90	5.5	4.6	0	8,439
2	Before	205	0.30	6.2	7.0	15	8,874
	After	217	0.24	6.3	8.9	13	7,650
3	Before	113	0.77	7.1	5.8	4	9,750
	After	55	1.33	7.5	3.4	−2	7,918
4	Before	157	0.50	6.0	9.7	41	8,833
	After	60	1.27	5.3	3.7	17	7,424
5	Before	124	0.66	6.5	6.8	−4	10,266
	After	110	0.76	5.8	7.0	−4	10,248
6	Before	196	0.36	4.5	9.2	26	9,480
	After	130	0.50	4.0	6.8	14	7,056
7	Before	150	0.55	4.8	10.9	−9	10,710
	After	116	0.76	5.6	8.5	7	11,125
8	Before	37	2.24	7.3	3.6	15	7,605
	After	41	2.20	7.4	3.7	18	8,487
9	Before	103	0.73	6.3	6.5	37	9,960
	After	116	0.73	6.5	7.1	24	10,010
Mean	Before	128 ± 55	0.77 ± 0.58	6.1 ± 0.9	7.1 ± 2.4	11.4 ± 21	9,205 ± 1,146
± SD	After	101 ± 54	0.97 ± 0.57	6.0 ± 1.1	6.0 ± 2.1	9.7 ± 10	8,706 ± 1,421
Significance		NS	$p \leq 0.05$	NS	NS	NS	NS

* Abbreviations used are: CBF, coronary blood flow; CVR, coronary vascular resistance; $CS\text{-}O_2$, oxygen content in coronary sinus blood; MV_{O_2}, myocardial oxygen consumption; MLE, myocardial lactate extraction; RPP, rate-pressure product; NS, not significant.

known. Our study examined the myocardial metabolic cost of protamine, specifically its effect on myocardial oxygen supply and demand.

It is important to describe the patients studied accurately; results obtained in one clinical hemodynamic setting may not apply to all patients. Each of our patients was judged to be completely revascularized by the surgeon. The study was limited to those patients who did not require vasoactive drugs including calcium after cardiopulmonary bypass. The mean pulmonary capillary wedge pressure was 14 mm Hg. The mean cardiac index of 2.25 L/min/m^2 indicates modest myocardial depression. None of the patients had evidence of an intraoperative myocardial infarction.

The cardiovascular effects of protamine in the dog have been described in detail (2–7). Consistently, a reduction in arterial blood pressure after protamine infusion is believed to be secondary to arteriolar dilation (3). This hypotension can be prevented by increasing blood volume before and during protamine administration (5, 6), and it is not affected by alpha- or beta-adrenergic blockade, blockade of autonomic ganglia, or depletion of endogenous histamine (7).

In contrast to the effects in the dog, the cardiovascular effects of protamine sulfate in man are more benign (8, 9). Conahan et al (9) infused protamine (3 mg/kg) over a 5-minute period in patients early after cardiopulmonary bypass, and found no alterations in heart rate, cardiac output, and central venous or arterial blood pressures. The only hemodynamic alteration in patients observed by Jastrzebski et al (8), following a 6-mg/kg protamine infusion, was an increase in mean pulmonary arterial pressure. They speculated this to be due to either pulmonary vasoconstriction, or secondary to obstruction of the pulmonary vascular bed by platelet microthrombi. We found no changes in pulmonary arterial pressure or resistance in our patients given 2.5 mg/kg of protamine.

We administered the protamine at a rate greater than the 50 mg/10 min that is usually recommended (15). Despite this rapid rate of infusion, no adverse alterations in hemodynamic variables were observed. No drugs were given nor changes in blood volume made during our study. However, our patients were doing well hemodynamically before protamine. The same dose and rate of infusion may produce significant circulatory depression in a more precarious condition. Our examination of myocardial metabolism revealed that protamine caused a small decrease in measured coronary blood flow, resulting in a corre-

sponding reduction in calculated myocardial oxygen consumption, as coronary sinus oxygen content remained unaltered. Myocardial lactate extraction showed no significant alteration. The significant increase in calculated coronary vascular resistance most likely reflects coronary vasoconstriction associated with a decrease in the myocardial oxygen demand (MV_{O_2}). However, as a control group with similar measurements was not examined, we cannot be positive that the small decrease in coronary blood flow and increase in coronary vascular resistance would not have occurred in the absence of protamine.

Statistical evaluation was performed using the Wilcoxon paired sample test. The hypothesis tested by the Wilcoxon test is that the two populations represented by the paired samples are identical. This test was used instead of the paired *t*-test because of the relatively small sample sizes. In order to provide an estimate of the power of the various comparisons, paired *t*-tests were also calculated (data not shown). Powers were calculated for the paired *t*-test from the observed differences between the means, for the given sample size, and assuming a level of significance (alpha) less than 0.05. Due to the small sample sizes and the relatively small observed differences between the means, the powers of the *t*-tests were low, ranging from 0.10 to 0.58.

Limitations of the technique for measuring coronary sinus blood flow used in this study have been summarized elsewhere (11, 16, 17). We feel that this technique provides meaningful information regarding the magnitude and direction of changes in coronary blood flow when measured sequentially in the same patients. A potential criticism relates to the validity of coronary blood flow determination by the thermodilution technique when right atrial pressure is elevated (18). In all patients, the positional stability of the catheter in the coronary sinus and the absence of major reflux into the mouth of the coronary sinus were assessed as suggested by Mathey et al (18).

Although the global mean lactate extraction by the left ventricle and the measured coronary sinus oxygen content did not change following protamine infusion, regional areas of anaerobic glycolysis may have been compensated for by continued aerobic energy metabolism elsewhere in myocardial muscle. Our study could not examine regional myocardial pathophysiology, and the effect of protamine on these parameters in the revascularized patient remains to be determined.

Protamine sulfate at rapid infusion rates is often given to patients following cardiopulmonary bypass. Our study indicates that this practice in patients with adequate cardiac function and circulation is not associated with an adverse alteration in hemodynamics or global myocardial metabolism.

ACKNOWLEDGMENTS

We would like to thank Drs. Aurelio Chaux, Alfonso Miyamoto, Hector Sustaita, Myles Lee, and Robert Kass for allowing us to include their patients in the study; Dr. William Shell for performing the lactate determinations; Dr. Harvey Brown for performing the blood gas co-oximetry measurements; JoAnn Prause for statistical analysis; and Helen Schamroth and Kathleen Farrington for their excellent secretarial assistance.

REFERENCES

1. Finlayson DC, Kaplan JA. Cardiopulmonary bypass. In: Kaplan JA, ed. Cardiac anesthesia. New York: Grune & Stratton, 1979: 427.
2. Jaques LB. A study of the toxicity of the protamine (salmine). Br J Pharmacol 1949;4:135–44.
3. Hurt R, Perkins HA, Osborn JJ, Gerbode F. The neutralization of heparin by protamine in extracorporeal circulation. J Thorac Surg 1956;32:612–9.
4. Goldman BS, Joison J, Austin WG. Cardiovascular effects of protamine sulfate. Ann Thorac Surg 1969;7:459–71.
5. Gourin A, Streisand RL, Greineder JK, Stuckey JH. Protamine sulfate administration and the cardiovascular system. J Thorac Cardiovasc Surg 1971;62:193–204.
6. Gourin A, Streisand RL, Stuckey JH. Total cardiopulmonary bypass, myocardial contractility and the administration of protamine sulfate. J Thorac Cardiovasc Surg 1971;61:160–6.
7. Fadali MA, Ledbetter M, Papacostas CA, Duke LJ, Lemole GM. Mechanism responsible for the cardiovascular depressant effect of protamine sulfate. Ann Surg 1974;180:232–5.
8. Jastrzebski J, Sykes MK, Woods DG. Cardiorespiratory effects of protamine after cardiopulmonary bypass in man. Thorax 1974;29:534–8.
9. Conahan TJ III, Andrews RW, McVaughn H III. Cardiovascular effects of protamine sulfate in man. Anesth Analg 1981;60:33–6.
10. Friesinger GC, Page EE, Ross RS. Prognostic significance of coronary arteriography. Trans Assoc Am Phys 1970;83:78–92.
11. Ganz W, Tamura K, Marcus HS, Donoso R, Yoshida S, Swan HJC. Measurement of coronary sinus blood flow by continuous thermodilution in man. Circulation 1971;44:181–95.
12. Marbach EP, Weil MH. Rapid enzymatic measurements of blood lactate and pyruvate. Clin Chem 1967;13:314–25.
13. Yang SS, Bentivoglio LG, Maranhao V, Goldberg H. From cardiac catheterization data to hemodynamic parameters. Philadelphia: FA Davis, 1972:37–43.
14. Winkler RL, Hays WL. Statistics: probability, influence and decision. New York: Holt, Rhinehart and Winston, 1975:842–5; 856–9.
15. O'Reilly RA. Anticoagulant, antithrombotic and thrombolytic drugs. In: Gilman AG, Goodman LS, Gilman A, eds. Pharmacological basis of therapeutics. New York: Macmillan, 1980: 1352.
16. Weisse AB, Regan TJ. A comparison of thermodilution coronary sinus blood flows and krypton myocardial blood flows in the intact dog. Cardiovasc Res 1974;8:526–33.
17. Simonsen S. Aspects of cardiac venous flow measured by continuous infusion thermodilution technique. Cardiology 1977;62:51–62.
18. Mathey DG, Chatterjee K, Tyberg JV, Lekven J, Brundage B, Parmley WW. Coronary sinus reflux: a source of error in the measurement of thermodilution coronary sinus flow. Circulation 1978;57:778–86.

ANESTH ANALG
1982;61:252-5

Transcutaneous P_{O_2} as a Trend Indicator of Arterial P_{O_2} in Normal Anesthetized Adults

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RAFFERTY, T. D., MARRERO, O., NARDI, D., SCHACHTER, E. N., MENTELOS, R., AND NGEOW, Y. F.: Transcutaneous P_{O_2} as a trend indicator of arterial P_{O_2} in normal anesthetized adults. Anesth Analg 1982;61:252-5.

The transcutaneous technique of measuring P_{O_2} (tcP_{O_2}) was studied in 30 adults with normal cardiovascular function undergoing nitrous oxide-enflurane or nitrous oxide-fentanyl anesthesia to determine the relationship between tcP_{O_2} and Pa_{O_2}. The tcP_{O_2} was an accurate and clinically useful trend indicator of Pa_{O_2} ($r = 0.9$; $p < 0.0001$). The ability to detect trends was unaffected by the type of anesthetic agent used. The technique was less useful in predicting absolute values for Pa_{O_2} ($r = 0.86$). It is suggested that more widespread application of such monitoring awaits definitive development of a halothane-resistant electrode.

Key Words: OXYGEN: tension, transcutaneous; MEASUREMENT TECHNIQUES: transcutaneous oxygen lesion; SKIN: transcutaneous oxygen tension.

THE VALIDITY of the transcutaneous technique of measuring arterial oxygen tension in adults has been established (1, 2). Oxygen electrodes are unaffected by the administration of nitrous oxide and enflurane (3). However, the reported intraoperative use of transcutaneous oxygen tension (tcP_{O_2}) monitoring of anesthetized adults has been scanty (4, 5). The following study was performed to delineate the relationship between tcP_{O_2} and Pa_{O_2} in adults with normal cardiac function anesthetized with N_2O-fentanyl or N_2O-enflurane.

Methods and Materials

Thirty adult patients (aged 17 to 68 years) without preoperative evidence of cardiac dysfunction were studied. Patient population, premedication, the anesthetic induction, intubation sequence, ventilatory management, monitoring procedures, and maintenance of anesthesia were previously described (6). Anesthesia was maintained with nitrous oxide and oxygen in a semiclosed system and supplemented with enflurane 0.5% to 1.5% in 15 of the patients and fentanyl, 5 to 15 μg/kg, intravenously in the remaining patients. The transcutaneous P_{O_2} sensor (model 818, Novametrix, Inc., Wallingford, CT) consisted of a Clark-type cathode and a silver anode covered by a 15-μ polypropylene membrane. The electrolyte was composed of a 0.2 M potassium borate solution with 95% ethylene glycol and 5% type II purified water. Electrode temperature was monitored by a thermistor and maintained at 45°C for reasons discussed below. Calibration was accomplished by exposing the sensor to preanalyzed 0% O_2 (5% CO_2/95% N_2) and 12% O_2 (10% CO_2/78% N_2/12% O_2), respectively. The sensors were positioned in the third or fourth intercostal space close to the sternum and fixed to the skin by means of an adhesive ring. The tcP_{O_2} values were continuously recorded on a polygraph recorder after calibration, and 20 minutes was allowed for the readings to stabilize. Transcutaneous measurements were compared with simultaneously obtained arterial blood gas values (Pa_{O_2}). Samples of arterial blood were drawn in heparin-rinsed (one unit per milliliter) plastic syringes and all air was expelled. Analysis was performed immediately using a standard blood gas ana-

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Received from the Departments of Anesthesiology, Epidemiology and Public Health, and Medicine, Yale University School of Medicine, New Haven, Connecticut. Accepted for publication October 26, 1981.

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lyzer (pH/blood gas analyzer #165, Corning Biomedical Instruments, Medfield, MA) at 37°C and corrected to body temperature (rectal) as necessary, the range of temperature being 35.6 to 37°C. The instrument was calibrated before each set of measurements. A two-point gas calibration [0% O_2 and 12% O_2 (gas calibration standard, Corning Biomedical Instruments)] was used in order that slowly responding electrodes and drift might be observed and to ensure that slope and zero adjustments were correctly made. Equilibrium was verified by the values repeating ±1 mm Hg. An aqueous control was run every 4 hours. This liquid-gas equilibration reference (Prime blood gas control, Fisher Scientific Co., Orangeburg, NY) consisted of human hemoglobin in a buffered matrix. A gas-to-liquid correction factor was not integrated into the measurements. Arterial samples were taken only when the transcutaneous curves had shown a steady state for at least 1 minute. The measurements were determined every 30 minutes for 3 to 6 hours. The minimum number of paired data points per patient was five; the maximum was 12. The study fulfilled Human Investigation Committee guidelines of the institution.

For trend analysis we computed the mean tcP_{O_2} and Pa_{O_2} for each patient and expressed each observation as the deviation from the respective mean ($TRtcP_{O_2}$ and $TRPa_{O_2}$) (7). This normalized the data and compensated for individual patient differences in the Pa_{O_2}-tcP_{O_2} gradient; these were specific and constant for each patient and thus irrelevant to analysis of relative changes, i.e., trends. In this context, this would be manifested by individual differences in intercept. Pearson correlation coefficient analysis was used to examine the tcP_{O_2}/Pa_{O_2} and $TRtcP_{O_2}/TRPa_{O_2}$ relationships. Regression analysis was used to compare the data of the patients receiving fentanyl with those obtained from patients given enflurane. The tests for coincidence and parallelism were used to test the hypotheses that the respective regressions were coincident and parallel.

Results

In the 30 patients 204 simultaneous tcP_{O_2} and Pa_{O_2} measurements were analyzed. When the fentanyl and enflurane data were analyzed separately, the tcP_{O_2} and Pa_{O_2} of each group were significantly related ($p < 0.0001$) with correlation coefficients of 0.88 and 0.85, respectively. The regression for the fentanyl data is given by the formula $Pa_{O_2} = 37.60 + 0.94\ (tcP_{O_2})$. The standard errors of the slope and intercept were 9.47 and 0.06, respectively. The regression for the enflurane data is given by the formula $Pa_{O_2} = 31.58 \pm 0.95\ (tcP_{O_2})$. The standard errors of the slope and intercept were 10.55 and 0.06, respectively. When the data of the fentanyl patients were compared with those of the enflurane patients, there was no evidence to reject the hypotheses that the regressions for fentanyl and enflurane were parallel ($p = 0.92$) and coincident ($p = 0.25$). Accordingly, the data sets were combined for the purposes of statistical analysis. The tcP_{O_2} and Pa_{O_2} of the combined fentanyl and enflurane data were significantly related ($p < 0.0001$) with a correlation coefficient of 0.86 (Fig 1). The regression is described by $Pa_{O_2} = 34.96 + 0.94\ (tcP_{O_2})$. The relationship between $TRtcP_{O_2}$ and $TRPa_{O_2}$ was also significant ($p < 0.0001$) with a correlation coefficient of 0.9 (Fig 2). This regression is described by $TRPa_{O_2} = -0.11 + 0.95\ (TRtcP_{O_2})$.

There were no untoward sequelae associated with monitoring of P_{O_2} in this study.

Clinical Use of TcP_{O_2} Monitor

Fig 3 depicts the decrease in tcP_{O_2} associated with tracheal retraction during an anterior cervical fusion. The changes in tcP_{O_2} associated with a stepwise decrement in F_{IO_2} are shown in Fig 4.

Discussion

Our data indicate that tcP_{O_2} was an accurate trend indicator of Pa_{O_2} in these patients with preoperatively normal cardiovascular function. This ability to detect trends was not affected by the type of anesthetic used.

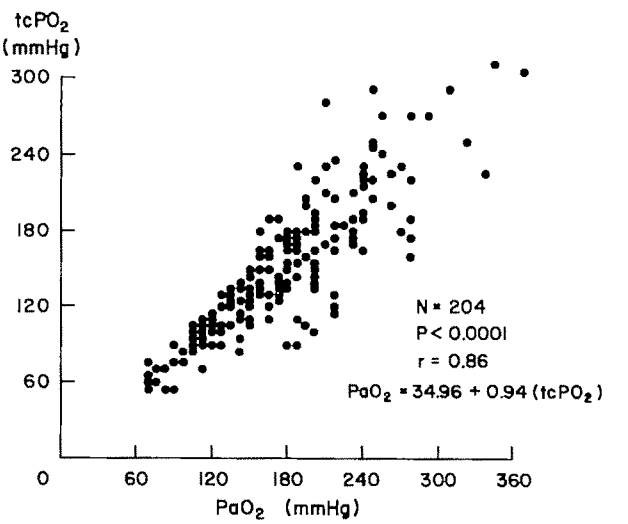


FIG 1. Relationship between transcutaneous (tcP_{O_2}) and arterial (Pa_{O_2}) measurements of oxygen tension.

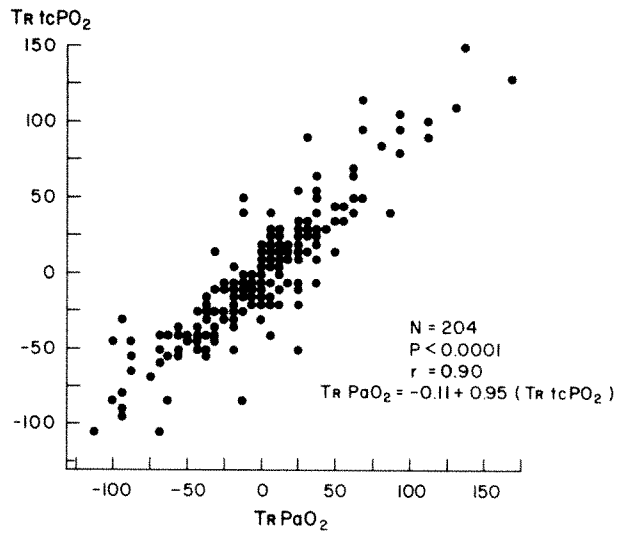


FIG 2. Relationship between $TRtcP_{O_2}$ and $TRPa_{O_2}$.

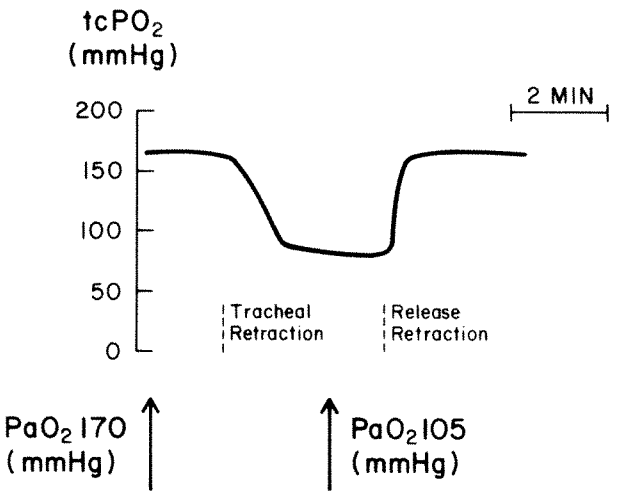


FIG 3. Changes in tcP_{O_2} associated with tracheal retraction during course of anterior cervical fusion in 67-year-old man undergoing N_2O-enflurane anesthesia.

The illustrative examples provided demonstrate the clinical utility of this noninvasive monitoring system. However, we found the technique to be less accurate in predicting absolute values of Pa_{O_2} and do not recommend it for that purpose. Rather, changes in tcP_{O_2} indicate when arterial blood gases also need to be drawn.

The normal epidermis appears to be oxygen deficient as oxygen is absorbed even at a low partial pressure (8). The outward loss of oxygen is negligible even to an atmosphere of pure nitrogen (8). To obtain a measurable cutaneous P_{O_2} the skin must be heated. This causes several effects that tend to increase the P_{O_2} at the skin surface. First, heating causes vasodilation of the dermal vessels, thus, arteriolizing the capillary blood. Second, heating causes a rightward shift of the oxyhemoglobin dissociation curve. Finally, heating may change the permeability coefficient for oxygen of the stratum corneum (9-11). It has been predicted from mathematical analysis of permeability data that the heating associated with an electrode temperature of 45°C (as used in this study) should compensate for the P_{O_2} gradient from the dermal vessels to the surface (11, 12). The tcP_{O_2} can be greater than Pa_{O_2} when the statum corneum is immature or not intact (13). In our series the tcP_{O_2} was invariably lower than the corresponding arterial value when the Pa_{O_2} was less than 150 mm Hg. However, the tcP_{O_2} was higher than the Pa_{O_2} in a large fraction of the determinations performed at a Pa_{O_2} greater than 150 mm Hg. This may be due to the inaccuracy of bench-type electrodes at high arterial oxygen tensions (14). However, it can be stated that a Pa_{O_2} of 150 mm Hg or greater was never associated with a tcP_{O_2} of less than 150 mm Hg, a finding which may be clinically useful.

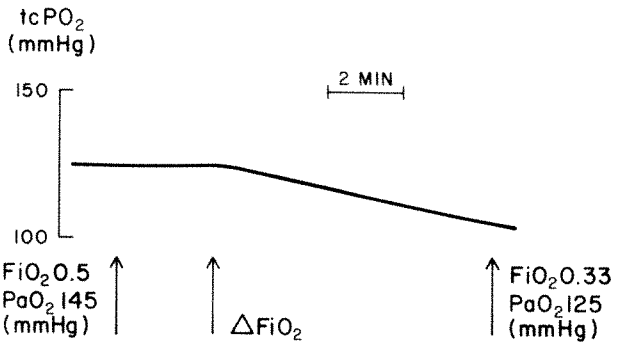


FIG 4. Transcutaneous P_{O_2} changes associated with decrease in $F_{I_{O_2}}$ in 66-year-old man undergoing N_2O-enflurane anesthesia for parietal craniotomy.

The correlation between transcutaneous and arterial blood gases is poor when cardiac function becomes compromised. The tcP_{O_2} no longer corresponds with the Pa_{O_2} when the cardiac output decreases to less than 1.9 L/min/m^2 (15, 16). Under these circumstances, the tcP_{O_2}-Pa_{O_2} gradient increases and the tcP_{O_2} corresponds with cardiac output ($r = 0.94$) and tissue oxygen delivery ($r = 0.96$) rather than Pa_{O_2} (15, 16). However, none of our patients had preoperative evidence of cardiac dysfunction and the lowest systolic blood pressure recorded was 90 mm Hg. Consequently, it is unlikely that systemic circulatory factors played a major role in this study.

For valid data comparison, a constant electrode placement site was used in our patients. The parasternal area was chosen emperically for ease of access; control studies may demonstrate that other sites are

more satisfactory. In addition, we have not formally studied the relationship between temperature and the Pa_{O_2}-tcP_{O_2} gradient. The narrow temperature range in our patients (vide supra) does not lend itself to valid statistical analysis. The effect of changes in body temperature on the measured tcP_{O_2} would be expected to depend on the efficiency of heat transfer from the annular heating element with the electrode and the underlying skin as well as on patient factors. Certainly the annulus-skin temperature gradient can vary considerably depending on transcutaneous P_{CO_2} electrode design and construction (17).

A disadvantage of this technique of gas analysis is that halothane interferes markedly with oxygen electrodes in vitro (3, 18). Although preliminary in vivo data using oxygen electrodes with Teflon membranes suggest that a halothane-resistant electrode system may become available (19), such an electrode has not yet been reported by independent investigators (20).

In conclusion, we found the transcutaneous method of blood gas analysis to be an accurate and clinically useful trend indicator of Pa_{O_2} in these anesthetized patients with normal cardiac function. The technique was less useful in predicting absolute values of Pa_{O_2}. We suggest that more widespread application of such monitoring awaits definitive development of a halothane-resistant electrode.

REFERENCES

1. Rooth G, Hedstrand U, Tyden H, Ogren C. The validity of the transcutaneous oxygen tension method in adults. Crit Care Med 1976;4:162–5.
2. Schonfeld T, Sargent C, Bautista D, et al. Transcutaneous oxygen monitoring during exercise stress testing. Am Rev Respir Dis 1980;121:457–62.
3. McHugh R, Epstein R, Longnecker D. Halothane mimics oxygen in oxygen microelectrodes. Anesthesiology 1979;50:47–9.
4. Huch R, Huch A. Transcutane Ueberwachung des arteriellen P_{O_2} in der anaesthesie: Einsatzfähigkeit der Methode am Beispeil von Kurznarkosen. Anaesthetist 1974;23:181–5.
5. Dennhardt R, Fraicke M, Mahal S, et al. Transcutaneous PO_2 monitoring in anaesthesia. Eur J Int Care Med 1976;2:29–33.
6. Rafferty TD, Marrero O, Nardi D, et al. Relationship between transcutaneous and arterial carbon dioxide tension in adult patients anesthetized with nitrous oxide-fentanyl and nitrous oxide-enflurane. Anesth Analg 1981;60:504–7.
7. Snedecor GW, Cochran WG. Statistical methods. 6th ed. Ames, IA: Iowa State University Press, 1967:172–95.
8. Shaw L, Messer A. Cutaneous respiration in man. III. The permeability of the skin to carbon dioxide and oxygen as affected by altering their tension in the air surrounding the skin. Am J Physiol 1931;98:93–101.
9. Van Duzee B. Thermal analysis of human stratum corneum. J Invest Dermatol 1975;65:404–8.
10. Michaels A, Chandvasekaran J, Shaw J. Drug permeation through human skin: theory and in-vitro experimental measurement. AIChE J 1975;21:985–96.
11. Tremper K, Huxtable R. Dermal heat transport analysis for transcutaneous O_2 measurement. Acta Anaesth Scand (Suppl) 1978;68:4–8.
12. Kimmich H, Kreuzer F. Model of oxygen transport through the skin as basis for absolute transcutaneous measurement of PaO_2. Acta Anaesth Scand (Suppl) 1978;68:16–9.
13. Huch R, Huch A, Albini M, et al. Transcutaneous PO_2 monitoring in routine management of infants and children with cardiorespiratory problems. Pediatrics 1976;57:681–90.
14. Tremper K, Waxman K, Bowman R, Shoemaker W. Continuous transcutaneous oxygen monitoring during respiratory failure, cardiac decompensation, cardiac arrest, and CPR. Crit Care Med 1980;8:377–81.
15. Sykes MK, Vickers MD, Eds. Principles of measurement for anaesthetists. Oxford: Blackwell Scientific Publications, 1973: 209.
16. Tremper K, Waxman K, Shoemaker W. Effects of hypoxia and shock on transcutaneous PO_2 values in dogs. Crit Care Med 1979;7:526–31.
17. Severinghaus J, Stafford M, Bradley A. $tcPCO_2$ electrode design, calibration and temperature gradient problem. Acta Anaesth Scand (Suppl) 1978;68:118–22.
18. Severinghaus J, Weiskopf R, Nishimura M, Bradley A. Oxygen electrode errors due to polarographic reduction of halothane. J Appl Physiol 1971;31:640–2.
19. Lane G, Samra S, Tait B, et al. How reliable is transcutaneous PO_2 during anesthesia. Anesthesiology (Suppl) 1980;53:S329.
20. Maekawa T, Okuda Y, McDowell D. Effect of low concentrations of halothane on the oxygen electrode. Br J Anaesth 1980;52:585–7.

ANESTH ANALG
1982;61:256-60

Arterial and Venous Dilation by Nitroprusside and Nitroglycerin—Is There a Difference?

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GERSON, J. I., ALLEN, F. B., SELTZER, J. L., PARKER, F. B., JR., AND MARKOWITZ, A. H.: Arterial and venous dilation by nitroprusside and nitroglycerin—Is there a difference? Anesth Analg 1982;61:256-60.

Whole-body arterial and venous dilating properties of nitroprusside and nitroglycerin were compared with each other in 20 adult patients during cardiopulmonary bypass for coronary artery bypass or valvular heart surgery and were compared with simultaneous forearm vascular measurements. Nitroprusside was found to be a more effective whole-body arterial vasodilator and nitroglycerin a better whole-body venous vasodilator when each drug was infused at rates of 1.5 and 2.0 μg/kg/min. No difference in whole-body vasodilation between the two drugs was found at 1.0 μg/kg/min. Forearm plethysmography did not distinguish between the two drugs at any dose level.

Key Words: ANESTHETIC TECHNIQUES: hypotensive, nitroprusside, nitroglycerin; ANESTHESIA: cardiovascular.

SODIUM NITROPRUSSIDE (SNP) is believed to cause both arterial and venous dilation, whereas nitroglycerin (NTG) is believed to be predominantly a venodilator (1, 2). The evidence for these differences in actions in man is incomplete. Venous dilation is either inferred from changes in ventricular pressure or from venous tone as measured by forearm plethysmography (1, 2). Objections may be raised to these approximations to the measurement of venodilation. First, changes in ventricular pressure might be due to changes in cardiac compliance rather than venodilation. Moreover, changes in the venous tone of the forearm, a single vascular bed, might not accurately reflect changes in the whole-body venous tone. The present study was undertaken to clarify these objections; changes in human whole-body venous dilation were examined without the confounding influence of the effects of SNP and NTG on the heart and on the pulmonary circulation.

Methods

Twenty adult patients undergoing elective open-heart operations gave informed consent to be studied. No patient received any drug for at least 11 hours before the study period except as described below. Anesthetic premedication was morphine, 0.15 mg/kg, and scopolamine, 0.004 mg/kg IM. General anesthesia was induced and maintained with fentanyl citrate to a total dose of 50 to 100 μg/kg. Succinylcholine infusion facilitated endotracheal intubation, whereas metocurine iodide, 0.15 to 0.45 mg/kg, provided intraoperative muscle relaxation. Fifteen patients received nitrous oxide; it was discontinued at least 15 minutes before cardiopulmonary bypass. Total, constant flow, cardiopulmonary bypass was established with the aorta cross-clamped and with snares tightened around the caval bypass cannulae. Bypass pump output was held constant throughout the study. Each patient then received SNP (Nipride, Hoffman-LaRoche) and NTG (Lilly, investigational drug) by pump infusion through polyethylene tubing into the venous reservoir of the oxygenator. During infusion, a steady state was assumed when mean arterial pressure (MAP) reached its nadir and remained stable for 3 minutes. Upon cessation of infusion, return of MAP to control level for at least 3 minutes was assumed to represent cessation of drug action. Each patient was

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studied in the following sequence: first control, first drug, second control, second drug. Control periods lasted approximately as long as drug periods. Order of administration of SNP and NTG was randomized. Patients received the same dose of SNP as of NTG at one of three randomly assigned dosage levels: 1.0, 1.5, or 2.0 μg/kg/min.

Changes in systemic vascular resistance (SVR) were calculated using data obtained from a radial arterial cannula, a central venous pressure catheter (CVP), and oxygenator pump output according to the formula:

$$\text{SVR (dyne·sec·cm}^{-5}) = \frac{\text{MAP (torr)} - \text{CVP (torr)}}{\text{Pump output (L·min}^{-1})} \times 80.$$

Changes in whole-body venous capacitance were inferred from the maximum observed decrease in level of blood in the oxygenator venous reservoir following infusion of SNP or NTG. Venous reservoir level change (ΔVR) is defined as the change observed in the volume of contents in the oxygenator's venous reservoir during a control or a drug infusion period. ΔVR is the volume (milliliters) remaining in the oxygenator venous reservoir at the conclusion of a control or drug infusion period minus the volume in the reservoir at the start of that period. A positive ΔVR implies transfer of fluid from the patient to the reservoir, whereas a negative ΔVR implies transfer of fluid from the reservoir to the patient. Increased venous capacitance causes a negative ΔVR.

Simultaneous with this, forearm vascular resistance (FVR) (torr·ml^{-1}·100 ml tissue^{-1}·min^{-1}) and forearm venous tone (FVT) (torr·ml^{-1}·100 ml tissue^{-1}) were measured using the acute occlusion method and the 2-minute equilibration period method, respectively, as described by Mason and Braunwald (3). We used a mercury-in-Silastic strain gauge plethysmograph (4) (Parks Electronics).

Using a nested analysis of variance (5), we tested for statistical significance of differences between the control data preceding infusion of each drug. Comparison of NTG to SNP was made by paired *t*-test.

Results

Mean (±SD) rectal temperature of subjects was 30.3 ± 1.8°C at the start of the study. It decreased 1.3 ± 2.0°C during the course of the study. Bypass pump flow during drug infusion periods was maintained nearly identical with flow during control periods. Control bypass pump flow, chosen in a standard clinical manner based on patient size and temperature, averaged 3306 ± 672 ml (mean ± SD). Mean deviation from control flow during drug infusion was only 7 ± 22 ml (mean ± SD). Although the same steady state of constant MAP for 3 minutes was achieved during infusion of both drugs, the duration of infusion required to achieve steady-state MAP differed. SNP steady-state MAP was achieved in 2.5 ± 1.1 minutes (mean ± SD), whereas NTG steady state required 3.3 ± 1.6 minutes (mean ± SD) ($p < 0.05$).

In Table 1 are listed control values for the two arterial variables, SVR and FVR, and for the two venous variables, ΔVR and FVT. Randomization into dose groups was successful as no difference in control values for any variable was found. Because of our concern that the first drug's effects might "hangover" into the second drug infusion despite return of MAP to control levels, we compared first control (i.e., before first drug infusion) values with second control (i.e., before second drug infusion) values. No difference was found for SVR, FVR, or FVT. ΔVR, on the

TABLE 1
Control Values*

Variable	Dose group					
	1.0 μg/kg/min (n = 7)		1.5 μg/kg/min (n = 7)		2.0 μg/kg/min (n = 6)	
	1st control	2nd control	1st control	2nd control	1st control	2nd control
SVR (dyne·sec·cm^{-5})	2013 ± 576	2390 ± 520	1561 ± 456	1880 ± 320	1503 ± 497	1792 ± 581
FVR (torr·ml^{-1}·100 ml tissue^{-1}·min^{-1})	38.9 ± 27.7	41.8 ± 19.9	32.1 ± 10.7	39.3 ± 35.4	32.9 ± 24.8	39.9 ± 25.2
ΔVR (ml)	−86 ± 212	+42 ± 180	−164 ± 75	−64 ± 76	−217 ± 147	+83 ± 214
FVT (torr·ml^{-1}·100 ml tissue^{-1})	20.4 ± 9.3	25.4 ± 12.0	26.8 ± 13.6	26.4 ± 4.9	20.5 ± 8.2	18.8 ± 9.7

* Values are means ± SD. Abbreviations used are: SVR, systemic vascular resistance; FVR, forearm vascular resistance; ΔVR, venous reservoir level change; FVT, forearm venous tone. Nested analysis of variance showed a significant difference between the first and second control states for ΔVR only ($p < 0.05$). No difference in control variables between dose groups was shown for any variable.

other hand, was consistently greater during the second control period compared with the first. This means less net transfer of fluid from the venous reservoir to the patient occurred during the second control period than during the first. In some instances, net fluid transfer was from the patient to the reservoir (positive ΔVR); but no difference was observed between dose groups as individual patient variation in ΔVR was quite large. The standard deviation of ΔVR was quite large compared with its mean value.

In Table 2 are reported drug effects on the arterial system. No consistent difference in FVR between SNP and NTG was detected in the forearm, at any dose, whereas SNP shows greater systemic arterial dilation than NTG at the higher two doses.

Analogous findings were obtained on the venous side of the circulation (Table 3). No consistent difference in FVT between SNP and NTG was found at any dose, whereas ΔVR was consistently more negative for NTG than SNP at the two larger doses. Thus, NTG increased body venous capacitance more than SNP, as more volume was lost from the venous reservoir to the patient during NTG infusion.

TABLE 2
Arterial Effects*

Variable	Dose (n)	Nitroprusside	Nitroglycerin
	μg/kg/min	%	
SVR	1.0 (7)	−5.6 ± 6.71	−6.0 ± 6.9
	1.5 (7)	−13.3 ± 13.4†	0.9 ± 16.0
	2.0 (6)	−18.2 ± 15.3†	2.0 ± 12.1
FVR	1.0 (7)	−2.8 ± 31.2	−19.7 ± 24.7
	1.5 (7)	−49.1 ± 29.0	−21.4 ± 43.3
	2.0 (6)	−22.7 ± 18.9	6.3 ± 49.2

* Values are mean % change from control ± SD. Abbreviations are defined in footnote to Table 1.

† $p < 0.05$, paired *t*-test.

TABLE 3
Venous Effects*

Variable	Dose (n)	Nitroprusside	Nitroglycerin
	μg/kg/min		
ΔVR (ml change from control)	1.0 (7)	−450 ± 300	−700 ± 499
	1.5 (7)	−136 ± 69†	−507 ± 351
	2.0 (6)	−325 ± 275†	−675 ± 303
FVT (% change from control)	1.0 (7)	−4.4 ± 34.3	−10.9 ± 14.7
	1.5 (7)	−27.0 ± 28.1	−22.3 ± 19.9
	2.0 (6)	−13.8 ± 17.4	−13.8 ± 27.6

* Values are means ± SD. Abbreviations are defined in footnote to Table 1.

† $p < 0.05$, paired *t*-test.

Discussion

This experimental model differs from other clinical situations with respect to anesthesia, surgery, and body temperature. But, because the subjects were vasoconstricted before administration of NTG and SNP, we feel the model is an appropriate one to test vasodilators. Furthermore, these drugs are often used in this same clinical setting. Hsu, Hickey, and Forbes (6) have previously used cardiopulmonary bypass to study peripheral vascular drug effects.

Lacking reliable measurements of blood SNP and NTG levels, we used hemodynamic criteria to define a steady state. As a hedge against unforeseen drug hangover effects, we randomized the order of drug administration.

Three minutes of MAP stability, which may be short for a laboratory experiment, was used to keep aortic cross-clamp (cardiac ischemic) time within the limits imposed by the surgery rather than extend this time to accommodate the study. Furthermore, 3 minutes of MAP stability correlates well with a stable clinical dose of SNP and NTG; infusion rates are usually changed clinically at more frequent intervals when these drugs are given to achieve some desired MAP value.

Control Values

Systemic vascular resistance was relatively high in our subjects although not different between the dose groups. It was, however, in the same range as values reported by Stanley and Webster (7), 21.8 ± 1.2 peripheral resistance units (or 1744 dyne·sec·cm^{-5}), observed during presumably normothermic fentanyl anesthesia (50 μg/kg). Control values of FVR were within the range reported by Mason and Braunwald (3), 24.2 to 52.0 torr·ml^{-1}·100 ml tissue^{-1}·min^{-1}.

FVT control values were more than twice as high as the mean of 9.5 ± 1.6 torr·ml^{-1}·100 ml tissue^{-1} observed by Mason and Braunwald (3) in awake subjects, a finding consistent with the predominantly venous constricting effect of cold (8).

One might expect control values of ΔVR to be zero at all times during the conditions of constant flow, total cardiopulmonary bypass that were obtained in this study. We observed a modest decrease in venous oxygenator volume (negative ΔVR during most first control periods). This decrease was less in the second control period for each dose level. Although the mean values for the second control period for 1.0 and 2.0 μg/kg/min are positive, implying an increase in venous reservoir volume, these mean values may not be

different from zero due to the large standard deviation. Thus, control ΔVR values did change from the first to the second control period, implying less loss from (and possibly a gain in) the oxygenator venous reservoir volume with time. This change may be accounted for by our use of clear fluid oxygenator prime. Vertees et al (9) found fluid absorbed by the patient averaged 50 ml/min during cardiopulmonary bypass lasting <90 minutes, decreasing to a mean of 42 ml/min during bypass lasting 90 to 150 minutes and to a mean of 37 ml/min during bypass lasting more than 150 minutes. Thus, decreasing patient uptake of venous reservoir volume is expected with time.

Accounting for those patients in the 1.0- and 2.0-μg/kg/min dose groups who actually lost volume to the venous reservoir (positive ΔVR) during the second control period is less clear. Possible, but unproven, explanations include venoconstriction from the 1.3 ± 2.0°C temperature decrease noted earlier, and a rebound vasoconstrictive effect following the first drug infusion. In any event, we feel the study design of randomizing order of drug administration should prevent bias in the interpretation of the experimental results below.

Experimental Results

SNP was the better systemic arterial dilator. We found SNP decreased SVR more than NTG at the higher two doses. This is in accord with the data of Stinson et al. (10). Simultaneously measured changes in FVR, however, were variable. No difference in effect on FVR was found between the two drugs.

Our data showed NTG to be a better systemic venodilator than SNP at the higher two doses. This is consistent with the data of Miller et al (2). No difference in effect on FVT between the two drugs was observed, a finding also consistent with Miller et al (2).

No dose-response relations are evident in our data. This lack of dose response is not surprising due to a number of factors. First, forearm variables FVR and FVT represent a mixed vascular bed whose components, muscle and skin, are affected in opposite directions by cold (11). Second, although we utilized infusion devices known to not bind NTG, the polyvinyl chloride arterial and venous tubing of the bypass circuit undoubtedly absorbed some NTG, potentially confounding the dose (12).

Third, and most important, the relatively large standard deviations for FVR, FVT, and ΔVR changes with SNP and NTG imply considerable patient-to-patient variability. This variability, inherent in data pooled from several subjects, together with a small sample size, may obscure any existing dose-response effect. But, the paired design of the study, wherein each patient received the same dose of SNP as of NTG, protects comparisons between the two drugs from this variability. The limitation of cardiac ischemic time imposed by surgery enabled us to study only two drug infusion periods and two controls per patient. This would be insufficient data for constructing a dose-response curve even if we had used two doses of the same drug.

The present study confirms in man the observation that SNP is a better whole-body arterial dilator than NTG, while showing NTG to be a better whole-body venous dilator than SNP. This finding has clinical applications. At equal doses, NTG would be expected to better decrease venous return to the heart and thus reduce preload or compensate for overtransfusion, whereas SNP would be expected to better decrease arterial blood pressure without decreasing venous return as much as NTG. The study also points out the fallibility in applying forearm plethysmographic data to the body as a whole. The forearm is only one of many vascular beds; changes in its arterial resistance and venous tone did not reflect the difference between NTG and SNP seen in the entire body.

ACKNOWLEDGMENT

Eli Lilly & Company graciously supplied nitroglycerin for use in this study.

REFERENCES

1. Armstrong PW, Walker DC, Burton JR, Parker JO. Vasodilator therapy in acute myocardial infarction: a comparison of sodium nitroprusside and nitroglycerin. Circulation 1975;52:1118-22.
2. Miller RR, Vismara LA, Williams DO, Amsterdam EA, Mason DT. Pharmacological mechanisms for left ventricular unloading in clinical congestive heart failure: differential effects of nitroprusside, phentolamine, and nitroglycerin on cardiac function and peripheral circulation. Circulation 1976;39:127-33.
3. Mason DT, Braunwald E. The effects of nitroglycerin and amyl nitrite on arteriolar and venous tone in the forearm. Circulation 1965;32:755-66.
4. Whitney RJ. The measurement of volume changes in human limbs. J Physiol 1953;121:1-27.
5. Zar JH. Biostatistical analysis. Englewood Cliffs, NJ: Prentice-Hall, 1974:144-7.
6. Hsu HO, Hickey RF, Forbes AR. Morphine decreases peripheral vascular resistance and increases capacitance in man. Anesthesiology 1979;50:98-102.
7. Stanley TH, Webster LR. Anesthetic requirements and cardiovascular effects of fentanyl-oxygen and fentanyl-diazepam-oxygen anesthesia in man. Anesth Analg 1978;57:411-6.
8. Shepherd JT. Role of the veins in the circulation. Circulation 1966;33:484-91.

9. Vertees RA, Stark M, Auvil J, Rohrer C, Rousou JH, Englemann RM. Weight gain and cardiopulmonary bypass. J Extra-Corporeal Technol 1980;12:74–8.
10. Stinson EB, Holloway EL, Derby G, et al. Comparative hemodynamic responses to chlorpromazine, nitroprusside, nitroglycerin and trimethaphan immediately after open-heart operations. Circulation (Suppl I) 1975;51,52:I-26–33.
11. VanHoutte PM. Physical factors of regulation. In: Bohr DF, Somlyo AP, Sparks HV Jr, eds. Handbook of physiology. Section 2: The cardiovascular system, vol II. Vascular smooth muscle. Washington, DC, American Physiological Society, 1980:462.
12. Ingram JK, Miller JD. Plastic absorption adsorption of nitroglycerin solution. Anesthesiology 1979;51:S132.

Cardiopulmonary Function following Transfusion

In order to evaluate the importance of red cell O_2 affinity of transfused blood on cardiac performance and adverse effects of transfusion on lung function, a prospective double-blind protocol was used in 27 patients undergoing abdominal aortic aneurysmectomy. Three types of blood were administered: packed red cells (PC), washed red cells (WC) and high 2,3-DPG red cells (2,3-DPG). An average of 4.5 units of blood was used per patient. Transfusion of 2,3-DPG blood resulted in maintenance of in vivo P_{50} during surgery and an increase to 31.2 torr after operation ($p < 0.001$). An intraoperative decrease in in vivo P_{50} to 23.2 ± 2.0 torr was observed in patients who were transfused with PC ($p < 0.001$) and to 25.1 ± 2.6 torr with WC ($p < 0.005$). After operation, in vitro P_{50} decreased in patients transfused with PC ($p < 0.005$) and WC ($p < 0.005$); it remained unchanged in the high 2,3-DPG group. This was consistent with the decrease of red cell 2,3-DPG in the PC ($p < 0.001$) and WC groups ($p < 0.01$) and maintenance in the 2,3-DPG group. Left ventricular stroke work and volume loading Starling-type myocardial performance curves were similar for the three groups. Microaggregates measured by Coulter counting and screen filtration pressure were the same for all three products in samples drawn on both sides of the 40-μm transfusion filter. There was no relationship of transfusion volumes or type of blood product to changes in lung function (physiologic shunting, dynamic compliance, and pulmonary arterial pressure) in the three groups of patients. It is concluded that 2,3-DPG enriched red cells improved oxygen availability, but that a 4.5 unit transfusion of any of the three blood products did not influence lung function or myocardial performance following aneurysmectomy. *(Krausz MM, Dennis RC, Utsunomiya T, et al. Cardiopulmonary function following transfusion of three red blood cell products in elective abdominal aortic aneurysmectomy. Ann Surg 1981;194:616–24)*

ANESTH ANALG
1982;61:261-6

Hemodynamic Consequences of Abrupt Withdrawal of Nitroprusside or Nitroglycerin following Induced Hypotension

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TODD, M. M., MORRIS, P. J., MOSS, J., AND PHILBIN, D. M.: Hemodynamic consequences of abrupt withdrawal of nitroprusside or nitroglycerin following induced hypotension. Anesth Analg 1982;61:261-6.

Nitroprusside (SNP) and nitroglycerin (TNG) are frequently used to control or reduce blood pressure during anesthesia and are reported to produce similar hemodynamic changes during infusion. However, few data are available concerning the cardiovascular changes following abrupt withdrawal of these drugs. In this study, two groups of five dogs, each anesthetized with halothane, received either SNP or TNG in amounts sufficient to reduce mean arterial blood pressure to 30% below control levels. Both groups were maintained at this level for 30 minutes, the drugs then being abruptly discontinued. Hemodynamic measurements were then repeated intermittently for an additional 120 minutes. Both groups demonstrated generally similar responses during the hypotensive period although cardiac output increased by 28% in the dogs given TNG but did not change in those given SNP. During recovery, however, mean blood pressure rapidly returned toward normal in dogs given SNP, but mean pulmonary arterial pressure increased 24% above control levels, and remained elevated. In contrast, dogs given TNG had a markedly slower recovery phase, with more than 2 hours required for mean blood pressure to approach control values. During this time, mean pulmonary arterial pressures never exceeded control levels. An attempt was made to correlate these changes with circulating plasma catecholamine levels. During drug infusion, both epinephrine and norepinephrine levels increased at least transiently. After SNP was stopped, both epinephrine and norepinephrine levels rapidly returned to control levels. By contrast, plasma norepinephrine levels remained significantly above normal in animals that had received TNG, in spite of persistently low mean blood pressure and mean pulmonary arterial pressure. These data indicate that the period following discontinuation of SNP or TNG is accompanied by very different hemodynamic changes, and that abrupt discontinuation of SNP, but not TNG, produces a rebound pulmonary hypertension unrelated to plasma levels of catecholamines. By contrast, prolonged vasodilation was noted after TNG. Therefore, these drugs are clearly not identical, and differences following discontinuation should be considered when choosing an agent for producing controlled hypotension.

Key Words: ANESTHETIC TECHNIQUES: induced hypotension.

INTRAVENOUS nitroprusside and nitroglycerin have been used to control or reduce electively arterial blood pressure during anesthesia (1-3), and to treat myocardial ischemia, ventricular failure, and valvular dysfunction (4-7). Numerous workers have examined the cardiovascular effects of these two drugs (2-4, 6-11), and at least one direct comparison of their actions during induced hypotension has appeared (3). However, relatively little attention has been paid to the changes that occur when the administration of these drugs is abruptly halted. Rebound arterial hypertension following the use of nitroprusside has been described (12), but investigations concerning cardiovascular responses following nitroglycerin are not available. In view of the growing concerns over the adverse effects of discontinuing various cardiovascular drugs (13) and because of the increasing use of vasodilators during anesthesia and surgery, particularly for the elective induction of hypotension, we undertook a direct comparison of the hemody-

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Received from the Department of Anesthesia, Harvard Medical School and Anesthesia Service, Massachusetts General Hospital, Boston, Massachusetts, and Department of Anesthesia, University of California, San Diego, School of Medicine, La Jolla, California. Accepted for publication November 6, 1981. Presented in part at the American College of Cardiology Scientific Session, Dallas, Texas, 1980.
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namic actions of intravenous sodium nitroprusside (SNP) and nitroglycerin (TNG) in dogs with particular emphasis on the first 2 hours following infusion.

Methods and Materials

Ten mongrel dogs, weighing 15 to 20 kg each, were studied. Anethesia was induced with thiopental, 20 mg/kg IV, and the trachea was intubated with a cuffed tube after a single dose of succinylcholine, 1 mg/kg. Ventilation was controlled at a tidal volume of 12 ml/kg and at a rate sufficient to maintain normocarbia ($Paco_2$ of 40 torr) using an inspired gas mixture of 1.5% halothane in oxygen. Paralysis was maintained with intermittent doses of intravenous pancuronium bromide (0.1 mg/kg initially, and 0.05 mg/kg as needed). After bilateral femoral cutdowns, catheters were threaded into the iliac artery and into the right atrium (guided by observation of the pressure trace), and a separate #7 French thermistor-tipped, triple-lumen Swan-Ganz catheter was floated into the pulmonary artery. Pressures were tranduced using Statham strain gauges, and recorded on a Grass polygraph. Monitored variables included phasic and electronically calculated mean arterial blood pressure ($\overline{BP}$ and BP), pulmonary arterial pressure (PAP and $\overline{PAP}$), pulmonary capillary wedge pressure ($\overline{PCWP}$), right atrial pressure ($\overline{RAP}$), and heart rate (HR, measured via a cardiotachometer coupled to the arterial pulse wave). Cardiac output (CO) was measured by thermodilution using an Edwards 9510A computer with injections made via the right atrial catheter. Esophageal temperature was maintained at 38°C with heat lamps, and arterial blood gas tensions were measured intermittently with Radiometer electrodes. Throughout the experiment, all animals received a constant intravenous infusion of lactated Ringer's solution at a rate of 3 ml/kg/hr.

After the animals had been stable for 45 minutes, they were alternately assigned to one of the two groups of five each. Dogs in group I received SNP, those in group II TNG. In each the protocol was identical. Drug infusion was begun after collection of control data and the dosage increased as needed to reduce $\overline{BP}$ slowly to a level 30% below control values, over a period of 35 to 45 minutes, and adjusted to keep $\overline{BP}$ stable at this value for an additional 30 to 35 minutes. Data were collected 5 minutes after achieving the desired degree of hypotension (30/1) and again at the end of the hypotensive period (30/2). Drug infusion was then abruptly halted, and measurements were taken 5, 15, 30, 45, 60, and 120 minutes later.

SNP was prepared fresh from the commercial drug (Nipride) at a concentration of 200 mg/L (in 5% dextrose in water). TNG was prepared by the hospital pharmacy as aqueous solution, 1 mg/ml, and was diluted before use to a concentration of 400 mg/L.

Arterial plasma concentrations of epinephrine (E) and norepinephrine (NP) were measured using a radioenzymatic technique (14, 15).

Systemic vascular resistance (SVR) was calculated as $(\overline{BP} - \overline{RAP})/CO$ and expressed as torr/liter/minute. Pulmonary vascular resistance (PVR) was calculated similarly, as $(\overline{PAP} - \overline{PCWP})/CO$ and reported in the same units. Stroke volume (SV) equalled CO/HR.

Statistical comparisons of changes from the control state were performed using a paired *t*-test. Due to the small sample size, specific note is made of *p* values falling between 0.1 and 0.05 in Figs 1 to 3. Intergroup testing was performed using the *t*-statistics for two means (unpaired *t*-test).

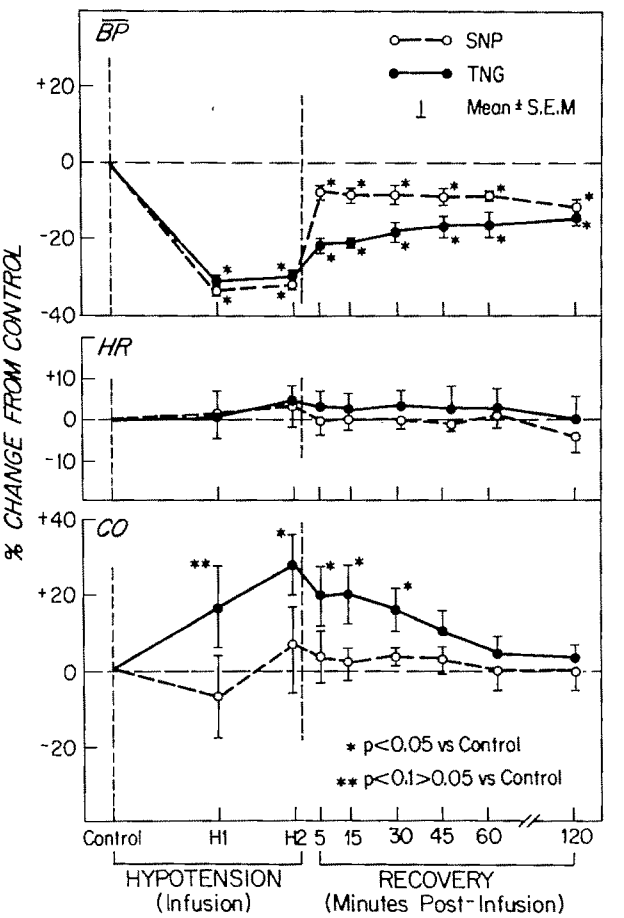


FIG 1. Changes in mean arterial blood pressure ($\overline{BP}$), heart rate (HR), and cardiac output (CO) both during and for 2 hours after drug infusion. Infusion was abruptly halted at time noted by vertical line. All values are expressed as percent change from control values.

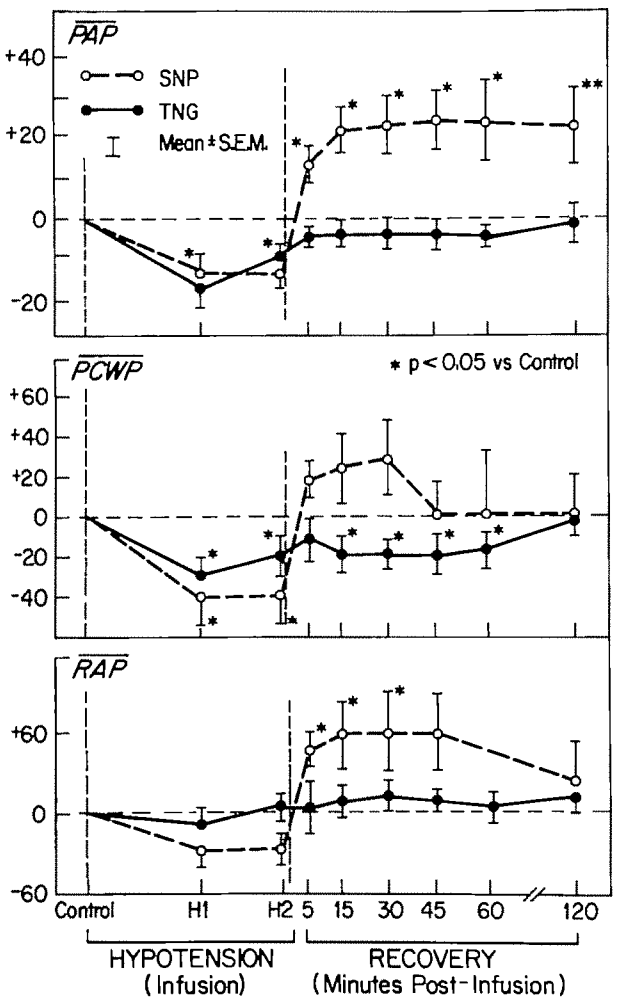


Fig 2. Changes in mean pulmonary arterial pressure (PAP), pulmonary capillary wedge pressure (PCWP), and right atrial pressure (RAP). Other notations as in Fig 1.

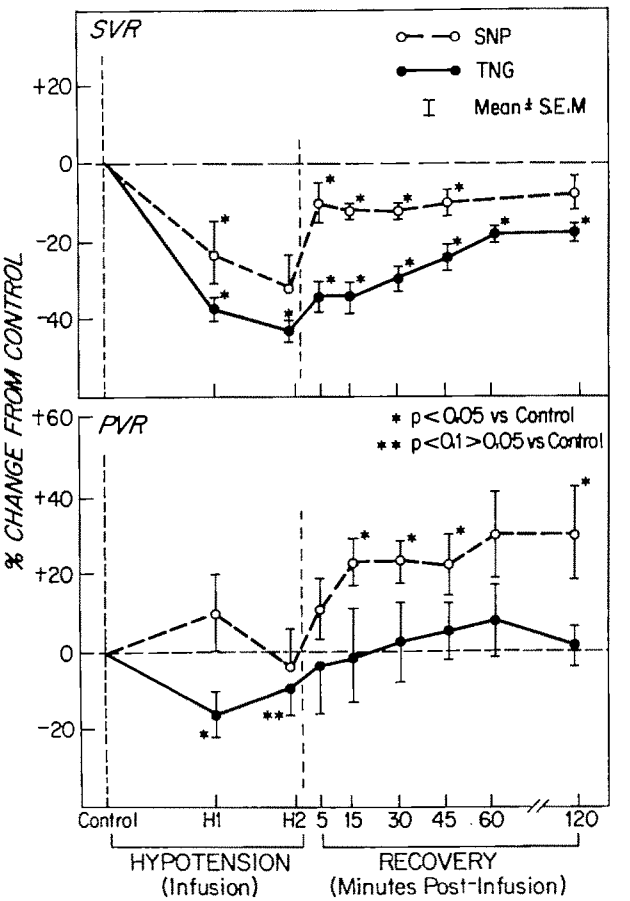


Fig 3. Changes in calculated systemic and pulmonary vascular resistances (SVR and PVR). Other notations as in Fig 1.

Results

SNP, 5.6 ± 1.2 (SEM) μg/kg/min, was required to achieve and maintain the desired maximum reduction in BP (30% below control levels), as compared with 79.8 ± 17.2 μg/kg/min of TNG. The largest single total dose of SNP given to any dog was 6 mg (36.5 μg/kg), and 95 mg (500 μg/kg) of TNG. There were no significant changes in Pa_{O_2}, Pa_{CO_2}, or pH in either group at any time.

Cardiovascular Changes—Hypotension

Control values for all measured variables in the two groups are given in the Table. There were no significant intergroup differences. Changes during and after drug infusion, expressed as percent changes from control values are presented in Figs 1 to 3.

Nitroprusside. SNP-induced hypotension was not accompanied by significant changes in HR or CO (Fig 1) and the reduction in blood pressure can be attributed entirely to a reduction in SVR (Fig 3). There were no changes in calculated stroke volume (not shown). Both PAP and PCWP decreased during infusion, but there were no changes in PVR. Changes in RAP were not statistically significant (Fig 2).

Nitroglycerin. In spite of comparable decreases in BP, TNG infusion was associated with a number of changes that differed from those seen with SNP. Although HR did not change, hypotension was accompanied by an increase in CO (Fig 1), which reached a maximum of +28% at the end of the hypotensive period, and by a decrease in SVR which reached a nadir of −42% (Fig 3). Both PAP and PCWP decreased, but the change in CO resulted in a significant decline in calculated PVR (Fig 2). Again, changes in RAP were insignificant.

Cardiovascular Changes—Recovery

Nitroprusside. Discontinuation of SNP was followed by a rapid increase in BP to a level approxi-

TABLE
Control Values for Measured Variables *

Variable	Control values	
	Nitroprusside (SNP)	Nitroglycerin (TNG)
$\overline{BP}$ (torr)	93.8 ± 3.1	86.3 ± 4.3
HR (beats/min)	119 ± 7	123 ± 6
CO (L/min)	2.9 ± 0.4	2.5 ± 0.2
SV (ml/beat)	24.3 ± 2.2	20.5 ± 1.7
$\overline{PAP}$ (torr)	13.1 ± 1.6	12.6 ± 0.3
$\overline{PCWP}$ (torr)	4.1 ± 1.2	5.5 ± 0.7
$\overline{RAP}$ (torr)	2.3 ± 1.0	2.8 ± 0.4
SVR (torr/L/min)	33.6 ± 4.7	34.8 ± 5.0
PVR (torr/L/min)	3.4 ± 0.8	2.9 ± 0.5
Pa_{O_2}	532 ± 65	577 ± 26
Pa_{CO_2}	40.4 ± 1.1	39.2 ± 0.6
pH	7.37 ± 0.01	7.39 ± 0.01
Epinephrine (pg/ml)	138 ± 48	119 ± 78
Norepinephrine (pg/ml)	157 ± 43	100 ± 41

* Values are means ± SEM. Abbreviations used are: $\overline{BP}$, mean blood pressure; HR, heart rate; CO, cardiac output; SV, stroke volume; $\overline{PAP}$, mean pulmonary arterial pressure; $\overline{PCWP}$, mean pulmonary capillary wedge pressure; $\overline{RAP}$, mean right atrial pressure; SVR, systemic vascular resistance; and $\overline{PVR}$, pulmonary vascular resistance. There were no intergroup statistical differences for any value (unpaired *t*-test).

mately 10% below control levels within 5 to 15 minutes (Fig 1). $\overline{BP}$ remained at this level for the remainder of the observation period. HR and CO remained at control levels and, as seen during infusion, the changes in $\overline{BP}$ were closely paralleled by changes in SVR (Fig 3). However, $\overline{PAP}$ increased rapidly to levels which exceeded control levels within 5 minutes, reaching a maximum of +24% between 30 and 60 minutes after discontinuation of the infusion (17.5 ± 1.9 torr with one dog reaching a maximum of 21.2 torr) (Fig 2). Although $\overline{PCWP}$ appeared to increase, this change was not statistically significant. $\overline{RAP}$ exceeded control values for the first 30 minutes of the recovery period, and PVR also increased, remaining elevated for the entire 2-hour period.

Nitroglycerin. Recovery from TNG was much less "dramatic" than that seen with SNP. The increase in $\overline{BP}$ was slow and progressive and both $\overline{BP}$ and SVR remained depressed with BP reaching levels comparable to those seen in dogs given SNP only after 2 hours (Fig 1). Similarly, $\overline{PCWP}$ remained below control levels until 2 hours (Fig 2) although $\overline{PAP}$ and PVR had normalized within 5 minutes (Fig 3). There were no changes in $\overline{RAP}$ following discontinuation of the infusion.

Plasma Catecholamines

Changes in arterial plasma levels of epinephrine (E) and norepinephrine (NE) are shown in Fig 4. As samples were not drawn at all times in all animals after discontinuation of the drug infusion, the results have been combined into two groups: samples drawn 5 or 15 minutes after halting the drug, and samples drawn after 30 minutes.

Control values in the two groups were similar (Table). In both, the induction of hypotension was accompanied by a significant increase in plasma E and NE (sample point 30/1) although 25 minutes later (sample point 30/2) E and NE levels in animals receiving SNP had returned to levels that were not statistically different from control values. Plasma NE levels were consistently greater in dogs given TNG. In all animals in both groups, values for E had returned to control levels within 5 to 15 minutes after discontinuation of the infusion and in dogs given SNP, NE levels had also returned to control values within 5 to 15 minutes. By contrast, plasma NE levels in dogs that had received TNG remained significantly elevated for the entire period after halting the drug.

Discussion

Our observations indicate that recovery from hypotension induced by SNP or TNG is accompanied by markedly different hemodynamic patterns. Of particular importance is the rebound pulmonary arterial hypertension seen in dogs given SNP. This increase in $\overline{PAP}$ pressure (and in calculated PVR) was associated with a transient increase in $\overline{RAP}$, suggesting some degree of right ventricular overload or dysfunction. There were no consistent signs of left ventricular abnormalities, nor did we observe systemic

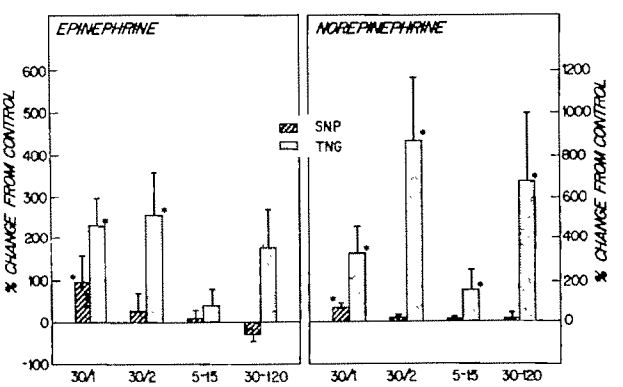


FIG 4. Changes in arterial plasma levels of epinephrine (right) and norepinephrine (left). All data are presented as percent change from control values. Note difference in scale for epinephrine and norepinephrine. As not all animals had samples drawn at all times after completion of infusion, data have been combined into those drawn 5 to 15 minutes, and 30 to 120 minutes after halting drug.

arterial hypertension. In contrast, $\overline{PAP}$ normalized in animals given TNG, and was accompanied by persistent arterial hypotension and reduced SVR.

Arterial hypertension following a sudden discontinuation of SNP has been described by several workers, both in animals (rats) and in humans (12, 16, 17), and Packer et al (16) have shown increases in $\overline{BP}$, $\overline{PCWP}$, $\overline{PAP}$, and $\overline{RAP}$ after stopping SNP in patients who had received the drug for treatment of severe congestive heart failure. Clinical conditions deteriorated in some of these individuals. The postulated mechanism for such rebound changes is felt to be the persistence of endogenous vasoconstrictors released as part of the normal response to hypotension, coupled with the rapid disappearance of SNP (12, 13, 16, 17). However, the identity of the responsible vasoconstrictors remains unclear. Khambatta et al (12) have shown that plasma renin activity remains elevated for some time after halting SNP. In keeping with a role for the renin-angiotension system, Delaney and Miller (17) noted that rebound arterial hypertension following SNP could be blocked by the infusion of the angiotension II antagonist saralasin. Although rebound arterial hypertension was not seen in these deeply anesthetized dogs, rebound pulmonary hypertension was observed. Our data at least indirectly suggest that circulating catecholamines do not play a role in these changes. Although E and NE levels increased at least transiently during drug infusion, the levels of both compounds returned quickly to control values at a time when pulmonary hypertension was at its maximum.

There are several unanswered questions raised by these experiments. The first concerns the lack of rebound arterial hypertension following SNP infusion, even though pulmonary arterial vasoconstriction was seen. This discrepancy between our work and that of others (12, 16, 17) cannot be explained easily. We did observe a rapid increase in $\overline{BP}$ and SVR after halting SNP, but these never exceeded control values. The absence of hypertension may have been species related, as other observations have been in either rats or man. Hypertension may also have been blunted by the rather deep level of halothane anesthesia, although why this did not blunt the pulmonary vascular changes is unclear. The pulmonary vascular bed may be more sensitive to the responsible vasoconstrictor than is the systemic circulation, although this is completely speculative. The changes in $\overline{PAP}$ and $\overline{PVR}$ are clearly not due to changes in arterial blood gas tensions, as these did not change significantly during or after drug infusion, and hypoxia (which might constrict the pulmonary vasculature) was never seen. The minimum Pa_{O_2} seen was approximately 400 torr.

The second question involves the lack of evident vasoconstriction following TNG. The two most likely explanations are: (*a*) the vasodilator effects of the drug persist long after its discontinuation; or (*b*) the compensatory response to its administration differs from that seen with SNP. There is some support for both of these possibilities. TNG is a highly lipid-soluble agent (18) and rather large doses were required to achieve and to maintain the desire degree of hypotension. The plasma half-life following a single sublingual dose of TNG is less than 10 minutes (18). However, the kinetics of continuous infusion is not well described, nor are the interactions of TNG with various anesthetics. Yei and Reid (19) were unable to find any correlation between the rate of intravenous TNG infusion and plasma levels of the drug. They did not study blood levels of TNG during the recovery phase. However, Armstrong et al (20) infused TNG into 16 patients (the end point was a 25% decrease in $\overline{PAP}$), for periods of approximately 30 to 60 minutes, and noted that the plasma half-life following termination of the infusion was only approximately 2 minutes. They also noted that hemodynamic recovery was much slower than the decrease in blood levels, but they did not study disappearance of TNG from the plasma in patients given much larger doses. It is therefore possible that some persistent vasodilation might be due to a drug that is bound to a site in the vessel wall. This possibility is supported by the recent observation that there is significant vascular uptake of TNG, particularly in the pulmonary vascular bed (21). Data from that study suggest that the failure to observe a rebound change following TNG may be simply due to a prolonged vascular effect, in contrast to the evanescent effects of SNP. However, it is possible that the compensatory vasoconstrictor responses produced during infusion were different. We noted that plasma levels of circulating E and NE were consistently higher during TNG infusion than during infusion of SNP, in spite of similar changes in $\overline{BP}$. However, we also noted persistently elevated NE levels during the recovery, which would be expected to produce vasoconstriction. These findings suggest that the changes in circulating catecholamines are occurring in a passive response to persistent drug-induced vasodilation. There are no data available concerning the response of the renin-angiotension system to the infusion of TNG.

In spite of these unanswered questions, our observations clearly demonstrate marked differences in the

hemodynamic patterns seen after discontinuation of these two drugs and suggest that they are not clinically interchangeable. As rebound pulmonary hypertension may not be accompanied by arterial hypertension, the adverse effects of halting SNP may go unnoticed unless pulmonary arterial pressure is being measured. These changes might be particularly detrimental in patients with preexisting pulmonary vascular or right ventricular disease. At the very least, a careful effort should be made to avoid sudden withdrawal (either intentional or accidental) of SNP. Conversely, the slow recovery from TNG (particularly after large doses) might be undesirable in situations in which rapid modulation or recovery of BP is required. These differences should therefore be taken into consideration when choosing a vasodilator for a given patient.

REFERENCES

1. Taylor TH, Styles M, Lamming AJ. Sodium nitroprusside as a hypotensive agent in general anaesthesia. Br J Anaesth 1970;42: 859–63.
2. Kaplan JA, Dunbar RW, Jones EL. Nitroglycerin infusion during coronary artery surgery. Anesthesiology 1976;45:14–21.
3. Fahmy NR. Nitroglycerin as a hypotensive drug during general anesthesia. Anesthesiology 1978;49:17–20.
4. Chiariello M, Gold HK, Leinback RC, et al. Comparison between the effects of nitroprusside and nitroglycerin on ischemic injury during acute myocardial infarction. Circulation 1976;54: 766–73.
5. Cohn JN, Franciosa JA. Vasodilator therapy of cardiac failure. N Engl J Med 1977;297:27–31, 254–8.
6. Chatterjee K, Parmley WW, Swan HJC, et al. Beneficial effects of vasodilator agents in severe mitral regurgitation due to dysfunction of subvalvular apparatus. Circulation 1973;48:684–90.
7. Stone JG, Faltas AN, Hoar PF. Sodium nitroprusside therapy for cardiac failure in anesthetized patients with valvular insufficiency. Anesthesiology 1978;49:414–8.
8. Styles M, Coleman AJ, Leary WP. Some hemodynamic effects of sodium nitroprusside. Anesthesiology 1973;38;173–6.
9. Pagani M, Vatner SF, Braunwald E. Hemodynamic effects of intravenous sodium nitroprusside in the conscious dog. Circulation 1978;57:144–51.
10. Berstein L, Friesinger GC, Lichtlen PR, Ross RS. The effect of nitroglycerin on the systemic and coronary circulation in man and dogs. Circulation 1966;33:107–16.
11. Christensson B, Nordenfelt I, Westling H, White T. Intravenous infusion of nitroglycerin in normal subjects. Scand J Clin Lab Invest 1969;23:49–53.
12. Khambatta HJ, Stone JG, Khan E. Hypertension during anesthesia on discontinuation of sodium nitroprusside-induced hypotension. Anesthesiology 1979;51:127–30.
13. Gerber JG, Nies AS. Abrupt withdrawal of cardiovascular drugs. N Engl J Med 1979;301:1234–5.
14. DaPrada M, Zurches G. Simultaneous radioenzymatic determination of plasma and tissue adrenaline, noradrenaline and dopamine within the femtomole range. Life Sci 1976;19:1161–74.
15. Pevler JD, Johnson GA. Simultaneous single isotope radioenzymatic assay of plasma norepinephrine, epinephrine and dopamine. Life Sci 1977;21:625–36.
16. Packer M, Meller J, Medina N, et al. Rebound hemodynamic events after the abrupt withdrawal of nitroprusside in patients with severe chronic heart failure. N Engl J Med 1979;301:1193–7.
17. Delaney TJ, Miller ED. Rebound hypertension after sodium nitroprusside prevented by saralasin in rats. Anesthesiology 1980;52:154–6.
18. Armstrong PW, Armstrong JA, Marks GS. Blood levels after sublingual nitroglycerin. Circulation 1979;59:588–92.
19. Yei JY, Reid PR. Quantitative determination of trinitroglycerin in human plasma. Circulation 1979;59:588–92.
20. Armstrong PW, Armstrong JA, Marks GS. Pharmacokinetic-hemodynamic studies of intravenous nitroglycerin in congestive cardiac failure. Circulation 1980;62:160–6.
21. Hill AB, DeRosayro AM, Nahrowold ML, Tait AR. Vascular uptake of nitroglycerin. Anesthesiology 1980;53:S82.

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1982;61:267-72

Anesthetic Induction with Alfentanil: A New Short-Acting Narcotic Analgesic

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NAUTA, J., DE LANGE, S., KOOPMAN, D., SPIERDIJK, J., VAN KLEEF, J., AND STANLEY, T. H.: Anesthetic induction with alfentanil: a new short-acting narcotic analgesic. Anesth Analg 1982;61:267-72.

Alfentanil, a new ultra short-acting, potent, synthetic narcotic was evaluated as an anesthetic induction agent in 20 unsedated, patients premedicated with atropine about to undergo general surgical operations with halothane-nitrous oxide anesthesia (group I) and in 22 patients premedicated with lorazepam and atropine [nine with mitral valvular disease (group II), and 13 with coronary artery disease (group III)], about to undergo open-heart surgery with alfentanil-oxygen anesthesia. Patients in groups II and III had radial and thermodilution pulmonary arterial catheters in place before anesthetic induction. Following pretreatment with pancuronium (1.5 mg/70 kg) and while breathing pure oxygen, alfentanil was administered intravenously at a rate of 50 μg/kg/min until the patient was unconscious. Cardiovascular dynamics were measured before and after pancuronium, at the point of unconsciousness, following succinylcholine paralysis, and 1 and 4 minutes after endotracheal intubation. The time of induction and the incidence of arrhythmias, chest wall rigidity, and pain on injection were also recorded. Loss of consciousness was rapid, 134 ± 28, 47 ± 19, and 75 ± 22 seconds in groups I, II, and III, respectively. Alfentanil resulted in a transient small decrease in systolic arterial blood pressure with loss of consciousness in groups II and III but no change in right atrial and mean pulmonary arterial pressures or cardiac output throughout the study period. Patients in group I had no change in any cardiovascular variable measured. The only significant undesirable side effect was chest wall rigidity, which occurred in 50% of group I and 22% and 31% of groups II and III, respectively. No patient remembered any aspect of laryngoscopy, endotracheal intubation, or surgery and only one thought the anesthetic induction was unpleasant. These data indicate that rapid infusion with alfentanil results in a rapid, pleasant anesthetic induction with little change in cardiovascular dynamics and a minimum of side effects.

Key Words: ANALGESICS: alfentanil; ANESTHETICS, Intravenous: alfentanil; ANESTHESIA: cardiovascular.

ALFENTANIL (*N*-[1-[2-(4-ethyl-4,5-dihydro-5-oxo-1H-tetrazol-1-yl)ethyl]-4-(methoxymethyl)-4-piperidinyl]-*N*-phenyl propanamide, Fig 1), is a new ultra short-acting, potent narcotic analgesic, which is being evaluated as an intravenous supplement during nitrous oxide anesthesia (1, 2). Alfentanil is chemically related to fentanyl but is one third as potent and has one third the duration of action of the latter. Data on animals suggest that alfentanil has a more rapid onset of action than fentanyl (3). Alfentanil is supplied as the aqueous solution of the hydrochloride salt in a concentration of 0.5 mg/ml. Alfentanil's rapid onset of action (one circulation time if given as a bolus), short duration of activity (less than 10 minutes following a single dose), and apparent benignity on circulatory dynamics suggest that it might be useful for induction of anesthesia (1-3). The objective of this investigation was to evaluate alfentanil as an anesthetic induction agent in patients with and without significant cardiovascular disease.

Methods

The protocol was approved by the Leiden University Human Experimentation Committee. Informed consent was obtained from each patient at the time of the preoperative visit.

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Supported in part by Stanley Research Foundation.

Received from the Departments of Anesthesiology, The University of Leiden Hospital, Leiden, The Netherlands, and The University of Utah Medical School, Salt Lake City, Utah. Accepted for publication November 12, 1981.

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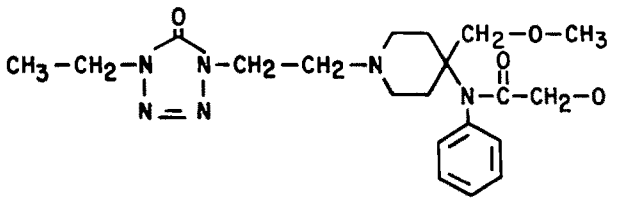


FIGURE. Structural formula of alfentanil.

Subjects included 20 patients (A.S.A. class I or II) without a history of cardiac, pulmonary, or renal disease about to undergo general abdominal surgical operations (group I), nine patients with severe mitral valvular disease (stenosis and/or insufficiency) about to undergo mitral valve replacement (group II), and 13 patients with coronary artery disease about to undergo coronary artery bypass grafting (CABG) operations (group III). Patients in group I were taking no preoperative medications, whereas all but one of those in group II were taking digoxin and one or more of a variety of diuretics. All patients in group III were taking propranolol and 10 patients were taking nitroglycerin or another oral vasodilator as well. Patients in group I were premedicated with atropine (0.1 mg/15 kg IM), whereas those in groups II and III were given lorazepam (0.08 mg/kg orally) and atropine (0.1 mg/15 kg IM). Lorazepam was administered 2 hours and atropine 30 minutes before arrival in the operating room. Patients taking propranolol received their usual dose of propranolol at the time lorazepam was given.

Upon arrival in the operating room catheters were placed in a hand vein in all patients and in a radial artery in patients in groups II and III. Patients in the latter groups also had an Instrument Laboratories (IL) thermodilution flow-directed balloon-tipped pulmonary arterial catheter (model 44166 7F) implanted percutaneously into their pulmonary artery via a basilic vein in the antecubital fossa. All patients had a bipolar lead II electrocardiogram continuously recorded. In group I, patients' systolic and diastolic arterial blood pressures were measured with a standard Riva Rocci blood pressure cuff, and heart and respiratory rates were determined by palpation of the radial artery and chest wall, respectively. In groups II and III heart rate was determined as in group I, whereas blood pressures (systolic and diastolic radial arterial and mean right atrial and pulmonary arterial) were measured using Statham pressure transducers. Cardiac output was determined (in duplicate) via a thermodilution technique using 10 ml of 5 to 10°C dextrose, 5%, in water as the injectate.

Following preparatory procedures and a 10-minute stabilization period, control cardiovascular dynamics were recorded and the patient was given 100% oxygen to breathe. Two minutes later pancuronium (1.5 mg/70 kg) was administered intravenously. Three minutes after pancuronium, alfentanil was administered intravenously at a rate of 50 μg/kg/min. (This administration rate was chosen following a pilot study evaluation of the incidence of rigidity and speed of induction at various rates of alfentanil infusion. The ideal rate of alfentanil infusion, in terms of minimizing chest wall rigidity and induction time, was found to be 50 μg/kg/min.) Respirations were first spontaneous, then assisted, and finally controlled, using a face mask and semiclosed system to maintain Pa_{CO_2} (as measured every 15 minutes via a radial arterial blood sample) and/or end-tidal P_{CO_2} (as continuously recorded via a sampling catheter in the Y-piece) at control (preanesthetic induction) values. During infusion of alfentanil, patients were commanded to open their eyes and take a deep breath every 5 to 10 seconds. Failure to respond to three consecutive commands was equated with unconsciousness. When unconscious, the patients were paralyzed with intravenous succinylcholine (1.5 mg/kg) and had their tracheas intubated with a cuffed Portex tracheal tube. After intubation patients in group I received halothane (0.2% to 1.0%) and nitrous oxide (60%) in oxygen as the only other anesthetic for the remainder of the operation, whereas patients in groups II and III received additional alfentanil (0.5 to 1.5 mg IV) if and when systolic arterial blood pressure or heart rate increased 15% or more above preanesthetic values. (Patients in groups II and III did not receive additional alfentanil until 5 minutes after intubation.)

Cardiovascular dynamics were recorded before and 3 minutes after pancuronium administration, at the moment of unconsciousness, 1 minute after succinylcholine (before tracheal intubation), and 1 and 4 minutes after tracheal intubation. Other variables evaluated during induction included: pain with alfentanil injection (patients were questioned during infusion and 24 hours after surgery; the presence of arrhythmias, the time to unconsciousness, the dose of alfentanil needed for unconsciousness, and muscle (chest wall) rigidity, evaluated as follows: no rigidity, no difficulty with manual positive-pressure ventilation and no clinical evidence of abdominal wall (as determined by palpation) or upper limb stiffness (as determined by manual elbow flexion); mild muscle rigidity, positive-pressure ventilation possible but with some difficulty associated with mild abdominal wall and/or upper limb stiffness; severe muscle rig-

idity, impossible to ventilate before succinylcholine administration and associated with marked abdominal wall and upper limb stiffness.

All patients were interviewed 24 to 48 hours after surgery. Questions were specifically directed at determining the last thing remembered during induction of anesthesia, any negative features of the induction period, and whether the patients remembered any aspect of laryngoscopy, tracheal intubation, or the operative procedure. Data were analyzed for statistical significance using Student's paired and unpaired *t*-tests and the chi-square test.

Results

The ages, weights, and preoperative diastolic blood pressures of patients in the three groups were similar (Tables 1 and 2). Patients in group I had significantly higher preoperative systolic arterial blood pressure than those in groups II and III and a significantly higher preoperative heart rate than patients in group III. (The significance of these differences between group I and groups II and III must be questioned because of the different methods used to measure blood pressure in group I.)

Patients in group I required 119 ± 20 μg/kg of alfentanil for unconsciousness, whereas those in groups II and III needed 41 ± 9 and 50 ± 10 μg/kg, respectively (Table 3). Average induction time was 134 ± 28 seconds in group I and 47 ± 19 and 75 ± 22 seconds in groups II and III, respectively. Differences between group I and groups II and III with respect to anesthetic dose and time for induction and between

TABLE 1
Preoperative Data*

Group	Age	Weight	Preanesthetic heart rate	Preanesthetic blood pressure	
				Systolic	Diastolic
	yr	*kg*	*beats/min*	*torr*	
I	42	72	85	143	70
	±10	±10	±9	±10	±9
II	48	73	78	128†	68
	±11	±9	±8	±11	±7
III	51	73	72†	130†	64
	±9	±8	±9	±9	±9

* Values are means ± SD.

† $p < 0.05$, Student's unpaired *t*-test, when compared with group I values at same time.

TABLE 3
Doses of Alfentanil Required for Unconsciousness and Operation and Anesthetic Induction Time*

Group	Alfentanil		Induction time
	Unconscious	Operation	
	μg/kg		*sec*
I	119 ± 20	119 ± 20	134 ± 28
II	41 ± 9†	746 ± 81†	47 ± 19†
III	50 ± 10†	1356 ± 120†‡	75 ± 22†§

* Values are means ± SD.

† $p < 0.01$, Student's unpaired *t*-test when compared with group I values at same time.

‡ $p < 0.01$, Student's unpaired *t*-test when compared with group II values at same time.

§ $p < 0.05$, Student's unpaired *t*-test when compared with group II values at same time.

TABLE 2
Cardiovascular Responses during Anesthetic Induction with Alfentanil*

	Group	Control	Pancuronium	Unconscious	Succinylcholine	Intubation at:	
						1 min	4 min
Heart rate (beats/min)	I	85 ± 9	96 ± 9†	103 ± 10†	105 ± 11†	109 ± 11†	86 ± 9
	II	78 ± 8	80 ± 7	70 ± 7	76 ± 7	72 ± 8	71 ± 7
	III	72 ± 9	76 ± 7	67 ± 6	69 ± 7	71 ± 8	68 ± 8
Systolic blood pressure (torr)	I	143 ± 10	153 ± 9†	153 ± 10†	154 ± 9†	158 ± 9†	137 ± 10
	II	128 ± 11	136 ± 8†	117 ± 9†	123 ± 8	124 ± 7	122 ± 8
	III	130 ± 9	137 ± 9†	118 ± 12†	121 ± 11	126 ± 11	123 ± 10
Diastolic blood pressure (torr)	I	70 ± 9	72 ± 8	69 ± 9	71 ± 8	73 ± 8	64 ± 7
	II	68 ± 7	72 ± 7	60 ± 10	63 ± 9	66 ± 8	65 ± 7
	III	64 ± 9	66 ± 8	61 ± 9	62 ± 7	64 ± 7	61 ± 8
Mean right atrial pressure (torr)	II	6 ± 2	6 ± 2	8 ± 3	8 ± 2	5 ± 2	6 ± 2
	III	8 ± 2	8 ± 2	9 ± 2	8 ± 2	9 ± 2	9 ± 2
Mean pulmonary artery pressure (torr)	II	17 ± 2	19 ± 2	16 ± 3	18 ± 2	18 ± 2	15 ± 2
	III	17 ± 2	17 ± 2	19 ± 3	19 ± 2	17 ± 2	16 ± 2
Cardiac output (L/min)	II	4.6 ± 0.5	5.2 ± 0.7	4.2 ± 0.7	4.4 ± 0.7	18 ± 2	4.2 ± 0.5
	III	6.0 ± 0.7	5.1 ± 0.8	5.8 ± 0.9	5.6 ± 0.8	17 ± 2	5.5 ± 0.7

* Values are means ± SD.

† $p < 0.05$, paired *t*-test when compared with control values.

groups II and III with respect to induction time were statistically significant (Table 3).

No patient in any group experienced pain upon intravenous injection of alfentanil and only one patient (group I) experienced a change in rhythm (ventricular extra systoles every fourth beat for 45 seconds during tracheal intubation) at any time during the study period (Table 4). Of patients in group I, 50% experienced some form of muscle (chest wall) rigidity during anesthetic induction. The incidence of chest wall rigidity was significantly less in groups II and III, 22% and 31%, respectively. Rigidity was severe enough to prevent totally positive pressure ventilation before administration of succinylcholine in five patients (four in group I and one in group III).

With the exception of systolic arterial blood pressure, which was slightly increased following pancuronium administration and slightly decreased at the moment at which unconsciousness first occurred, no other cardiovascular variable was significantly changed at any time during the study in patients in groups II and III (Table 2). (Pulmonary capillary wedge pressures (PCWP) are not reported because in a few patients it was not possible to wedge the catheter, perhaps because of its long course from the antecubital fossa. In the remainder of patients, PCWP remained unchanged throughout the study.) Patients in group I experienced slight but significant increases in heart rate and systolic arterial blood pressure following administration of pancuronium; the increases were maintained until 4 minutes following intubation (when anesthesia was being maintained with halothane and nitrous oxide).

Operative times averaged 126 ± 41, 297 ± 50, and 357 ± 39 minutes in groups I, II, and III, respectively. All patients in group I could be extubated at the end of the operation (without need of a narcotic antagonist) and all were responding to verbal command upon entrance to the recovery room. When interviewed after surgery, all patients related that the last thing they remembered was either coming to the operating room or having a mask placed on their face and the first thing, after anesthesia, was their presence in the operating or recovery rooms. No patient in the study remembered laryngoscopy, tracheal intubation, or any aspect of the operative procedure. However, one patient in group I did recall being stiff just before unconsciousness and it frightened her. This patient was the only one who indicated that induction of anesthesia was an unpleasant experience.

TABLE 4
Anesthetic Induction Data

Group	% of patients with:				
	Pain on injection	Chest wall rigidity			Arrhythmias
		Mild	Severe	Total	
I	0	30	20	50	5
II	0	22	0	22*	0
III	0	23	0	31*	0

* $p < 0.025$, chi-square test when compared with group I value.

Discussion

An ideal agent for induction of anesthesia should provide a rapid but pleasant loss of consciousness with minimal cardiovascular alterations, possess no side effects, and have a short duration of action (5–7). Although there is, at this time, no ideal anesthetic induction agent, intravenous thiopental comes closest to being ideal and as a result is the most popular of the induction agents available and the standard to which all others are compared (7, 8). Unfortunately, thiopental is a myocardial depressant, possesses some undesirable side effects, and has no analgesic action (7). Some synthetic narcotic compounds (fentanyl and sufentanil), when administered intravenously as a rapid infusion or as a bolus, result in a rapid, pleasant onset of unconsciousness, produce little change in cardiovascular dynamics, block unwanted increases in arterial blood pressure and heart rate secondary to tracheal intubation (probably due to their profound analgesic properties), and have few side effects (9–11). Unfortunately, these compounds have a long duration of action and when administered in doses that produce unconsciousness result in anesthesia and respiratory depression for 8 to 14 hours (9, 11–13).

Alfentanil is a new short-acting, potent narcotic analgesic, closely related to fentanyl, which has a rapid onset and short duration of action (1–3). The results of this study demonstrate that when given as a fast intravenous infusion, alfentanil produces unconsciousness rapidly and with little alteration in cardiovascular dynamics either before or after tracheal intubation. Our findings also suggest that side effects of alfentanil are minimal.

Preliminary investigations by us (S. de Lange and T. H. Stanley, unpublished data, 1980) and J. de Castro (personal communication, 1979) have shown that alfentanil, when given in a bolus of 0.3 mg/kg, produces unconsciousness in less than 45 seconds (in patients with a normal cardiovascular system) and when combined with pancuronium (1.0 mg/10 kg) is not associated with chest wall rigidity. Induction of

anesthesia was conducted with a fast infusion of alfentanil rather than a bolus dose in this study because the cardiovascular actions of the drug in patients with heart disease were unknown. A bolus dose of pancuronium was omitted during the induction to minimize cardiovascular alterations produced by the muscle relaxant. However, we felt it was necessary to administer a small amount of pancuronium before alfentanil to prevent the high incidence of chest wall rigidity (80% to 90%) that we and others have found when a non-depolarizing muscle relaxant is completely omitted before rapid infusion of alfentanil, fentanyl, or any of the fentanyl-like narcotics (10–13).

Our results could be interpreted to indicate that premedication with lorazepam increases the speed of anesthetic induction (decreases alfentanil requirements for unconsciousness) and decreases the incidence and severity of muscle rigidity. In support of this conclusion, a reduced requirement for fentanyl during open heart surgery has been reported in patients with valvular disease when diazepam is added to the anesthetic regimen (2). Similarly, one of us (T. H. Stanley, unpublished data, 1980) has found that a benzodiazepine premedication reduces the incidence and severity of muscle rigidity following large, rapidly infused doses of fentanyl and sulfentanil. However, the differences in speed of anesthetic induction and increase of rigidity between group I and groups II and III in this study may also be related to cardiac pathology and/or preoperative drug therapy of the latter groups.

The influence of lorazepam on alfentanil requirements, on the incidence and severity of rigidity, and on cardiovascular alterations might have been better defined if all groups were subdivided into patients who did and did not receive lorazepam for premedication. The reason this was not done in group I patients was that many clinicians experienced with the narcotics and benzodiazepines are of the opinion that they potentiate and prolong each other when combined (14). We were concerned that if this occurred in group I patients, some of them having short (<1 hour) operations might require postoperative mechanical ventilation. Our fears were confirmed when one patient in group I (subsequently excluded from the study) accidentally received lorazepam (4.5 mg orally) as premedication 2 hours before a 70-minute operation. He required mechanical respiratory assistance for 110 minutes after surgery because of inadequate tidal volumes, although he was responsive to command. Lorazepam was not omitted from patients in groups II and III because it was considered unethical to omit all hypnotic premedication in patients about to be subjected to major invasive monitoring in an unanesthetized state. Although the role of lorazepam in producing the different responses to alfentanil in the three groups is clouded by absence of control (no lorazepam) and lorazepam subgroups within each group, it is our opinion that differences in physical status, medical condition, and preoperative drug therapy between groups I and III are small enough, that although not ideal, group I might be considered a control group for group III (at least with respect to the incidence of side effects such as muscle rigidity).

In this study, pretreatment with pancuronium significantly increased systolic arterial blood pressure in all groups and heart rate in group I. These changes are probably the result of the cardiac vagolytic action of pancuronium (15). Although increases in systolic blood pressure and heart rate following pancuronium were usually not marked, especially in groups II and III, they must be considered a negative feature of this induction technique. In contrast, the absence of further increases in these variables, as well as any change in systemic diastolic, right atrial, and pulmonary artery pressures and cardiac output throughout the remainder of the study are significant advantages of an alfentanil anesthetic induction, especially in patients with cardiac disease.

Pain on injection and thrombophlebitis were not problems in this study, probably because, in contrast to many hypnotics, alfentanil is water soluble. One side effect of alfentanil, which was present in all three groups and which always seems to be a potential problem during narcotic anesthetic induction, if a muscle relaxant is not concurrently used, is chest wall rigidity. Fortunately, patients are rarely aware of the rigidity and severe rigidity is uncommon, especially if the alfentanil infusion is administered at a rate of 50 μg/kg/min or less. Furthermore, rigidity, when it occurs, can be easily and rapidly corrected by the intravenous administration of succinylcholine.

Although evaluation of the incidence and severity of rigidity would have been improved if a group of patients who were not pretreated with pancuronium were also included in this study, we chose not to do so for a number of reasons. First and foremost was that preliminary experiences with the use of a rapid infusion of alfentanil showed that it produced a high incidence of rigidity (80% or greater) when pretreatment with a non-depolarizing muscle relaxant was omitted. This is also true with a rapid infusion of fentanyl and probably with all of the fentanyl-related narcotics (10). Second, we were unsure whether the

presence of rigidity might interfere with adequate determination of loss of consciousness. Third, because we were evaluating alfentanil as an induction agent for the first time in man, we felt obliged for ethical reasons to attempt to minimize a known undesirable side effect.

In conclusion, alfentanil administered as a fast intravenous infusion, especially following premedication with atropine and lorazepam and pretreatment with a small dose of pancuronium, results in a rapid, pleasant anesthetic induction with little change in cardiovascular dynamics, a speedy recovery (following halothane-nitrous oxide anesthesia), and a minimum of side effects.

REFERENCES

1. Kay B, Stephenson DK. Alfentanil (R 39209): initial clinical experience with a new narcotic analgesic. Anaesthesia 1980;35: 1197–1201.
2. Kay B, Pleuvry B. Human volunteers studies of alfentail (R 39209), a new short-acting narcotic analgesic. Anaesthesia 1980;35:952–6.
3. de Castro J, Van de Water A, Wouters L, et al. A comparative study of cardiovascular, neurological and metabolic side effects of elght narcotics in dogs. Acta Anaesthesiol Belg 1979;30:5–99.
4. Deleted in proof.
5. Wynands HE, Bhambhami M. A clinical comparison of diazepam and thiopentone as induction agents to general anaesthesia. Can Anaesth Soc J 1968;15:281–90.
6. McClish A. Diazepam as an intravenous induction agent for general anaesthesia. Can Anaesth Soc J 1966;13:562–75.
7. Guerra F. Thiopental forever after. In: Aldrete JA, Stanley TH, eds. Trends in intravenous anesthesia. Chicago: Year Book, 1980:143–51.
8. Dundee JW. The ideal intravenous anesthetic(s). In: Aldrete JA, Stanley TH, eds. Trends in intravenous anesthesia. Chicago: Year Book, 1980:127–42.
9. Bovill JG, Sebel PS. Pharmacokinetics of high-dose fentanyl: a study in patients undergoing cardiac surgery. Br J Anaesth 1980;52:795–802.
10. Hill AB, Nahrwold ML, de Rosayro AM, et al. Prevention of rigidity during fentanyl-oxygen induction of anesthesia. Anesthesiology 1980;53:S86.
11. de Lange S, Stanley TH, Boscoe MB. Comparison of sufentanil-O_2 and fentanyl-O_2 anesthesia for coronary artery surgery. Anesthesiology 1980;53:S64.
12. Stanley TH, Webster LR. Anesthetic requirements and cardiovascular effects of fentanyl-oxygen and fentanyl-diazepam-oxygen anesthesia in man. Anesth Analg 1978;57:411–6.
13. de Castro J. Practical applications and limitation of analgesic anaesthesia. Acta Anaesthesiol Belg 1976;27:107–28.
14. Stanley TH. Pharmacology of intravenous narcotic anesthetics. In: Miller RD, ed. Anesthesia. New York: Churchill Livingstone, 1981:438–50.
15. Saxena PR, Bonta IL. Specific blockade of cardiac muscarinic receptors by pancuronium bromide. Arch Int Pharmacodyn Ther 1971;189:410–2.

Increased Renal Clearance of Digoxin during Acute Vasodilator Therapy

The effect of vasodilator therapy on renal digoxin clearance in patients with chronic congestive heart failure was studied. intravenous administration of nitroprusside or hydralazine to eight patients with severe heart failure produced the expected increase in cardiac output and a decrease in central circulatory pressure. Renal clearance of sodium para-aminohippurate and estimated renal blood flow increased without a change in glomerular filtration rate. Total renal clearance of digoxin increased by 50% during vasodilator therapy. Thus, acute administration of vasodilator increases renal digoxin clearance without changing glomerular filtration rate, suggesting an increase in tubular secretion of digoxin. Long-term vasodilator therapy may alter the maintenance dosage of digoxin for optimal treatment of patients in congestive heart failure. *(Cogan JJ, Humphreys MH, Carlson CJ, Benowitz NK, Rapaport E. Acute vasodilator therapy increases renal clearance of digoxin in patients with congestive heart failure. Circulation 1981;64:973–6)*

ANESTH ANALG
1982;61:273–8

Hypotensive Effects of Adenosine and Adenosine Triphosphate Compared with Sodium Nitroprusside

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FUKUNAGA, A. F., FLACKE, W. E., AND BLOOR, B. C.: Hypotensive effects of adenosine and adenosine triphosphate compared with sodium nitroprusside. Anesth Analg 1982;61:273–8.

Hypotensive effects of the intravenous injection of adenine compounds [adenosine triphosphate (ATP), adenosine] were compared with those of sodium nitroprusside (SNP) in rabbits during light, stable halothane anesthesia. ATP and adenosine were almost equipotent in their effects on blood pressure and heart rate. The hypotensive potencies of ATP and adenosine were approximately 1/8 (bolus injection) and 1/40 (continuous infusion) that of SNP, but the adenine compounds had a more rapid onset of action and shorter recovery times than SNP. With bolus injection, SNP invariably caused a baroreceptor-mediated reflex increase in heart rate. In contrast, ATP and adenosine caused a dose-related decrease in heart rate and hypotension. With continuous infusion, ATP and adenosine produced immediate onset of hypotension without tachycardia. Blood pressure remained remarkably stable throughout the infusion; neither tachyphylaxis nor rebound hypertension were observed. Thus, the adenine compounds offer possible advantages over SNP as they are physiologic agents with little or no acute toxicity and may be devoid of tachycardia, tachyphylaxis, and rebound hypertension.

Key Words: ANESTHETIC TECHNIQUES: hypotensive; PHARMACOLOGY: adenosine triphosphate, adenosine, sodium nitroprusside.

THE EXTRACELLULAR, especially cardiovascular, effects of adenosine triphosphate (ATP) and related compounds [adenosine diphosphate (ADP), adenosine monophosphate (AMP), and adenosine] have been the subject of considerable research since they were first reported by Drury and Szent-Györgyi in 1929 (1) and studied in more detail by Green and Stoner (2). During the 1950s adenine nucleotides and nucleosides were the subject of intense pharmacologic and even therapeutic interest (3), but since then work has been focused more on biochemical and potential physiologic aspects of these compounds (4–6).

In recent years, the use of rapidly acting vasodilators for acute control of blood pressure in surgical patients, in cardiac patients, and in intensive care medicine has become widespread and clinically important. The drugs used for this purpose have been almost exclusively sodium nitroprusside (SNP) and to a lesser extent nitroglycerin (7–9). In Japan, ATP has also been used for this purpose (10–13), and recently some relevant animal observations have been reported (14, 15). However, the results of these (10–15) and earlier (3) studies with adenosine and ATP have been divergent, apparently because of the use of different experimental models and methods, including unstable background anesthesia. Thus, there exists a need for better characterization of the pharmacologic effects of adenosine and ATP as used to produce hypotension under well defined experimental conditions and with modern, clinically used, anesthetics.

The present study was designed to examine the hypotensive effects of adenosine and ATP in comparison with sodium nitroprusside during light halothane anesthesia.

Methods

Male New Zealand White rabbits (2.5 ± 0.01 kg each) were anesthetized with halothane by face mask. The tracheas were intubated with cuffed pediatric 2.5-mm tracheal tubes. The animals were then immobilized with pancuronium bromide, 0.1 mg/kg, given

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Received from the Department of Anesthesiology, Harbor-UCLA Medical Center, Torrance, California; and Department of Anesthesiology, University of California, Los Angeles, Center for the Health Sciences, Los Angeles, California. Accepted for publication November 17, 1981. Presented in part at the Annual Meeting of the American Society of Anesthesiologists, October 1980, St. Louis, Missouri.
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intravenously as needed, and the lungs ventilated via a constant-volume ventilator (Harvard Apparatus, model 661) to maintain $Paco_2$ at 30 ± 2 torr. Anesthesia was maintained with halothane, 1 vol% in oxygen, vaporized through a calibrated vaporizer. The right femoral artery was catheterized and connected to a strain gauge pressure transducer (Gould Statham P 23 ID). Arterial blood pressure and heart rate were recorded on a polygraph (Grass, model 79 D). Left and right ear veins were cannulated for administration of fluids and drugs. After establishment of steady-state anesthesia, the three agents (ATP, adenosine, and SNP) were administered intravenously in random order. Between drugs, blood pressure and heart rate were allowed to recover and stabilize for 15 minutes before the next drug administration. As the actions of these drugs are of extremely short duration, we evaluated the effects of both intravenous bolus injection (n = 13) and continuous infusion (n = 7) upon the blood pressure and heart rate. To determine the bolus injection dose needed to reduce mean arterial pressure by 40%, sequentially increasing doses of each drug were given allowing for complete recovery of blood pressure and heart rate. For continuous infusion, using an infusion pump, each drug was titrated to decrease the pressure and the dose was adjusted to induce approximately 45% hypotension. In order to compare the time course of action of each drug, the onset of action (from injection to maximum effect) and the recovery time (80% recovery of blood pressure after termination of infusion) were measured. Values are reported as means ± SEM. The data were analyzed using Student's t-test for paired data and $p < 0.05$ was considered statistically significant.

Adenosine triphosphate-Na_2 (ATP) (Kyowa Hakko, Japan), adenosine (Sigma), and sodium nitroprusside (SNP) (solution made up by the UCLA pharmacy in a 20-mg/ml solution, kept refrigerated in dark bottles) were diluted in physiologic saline solution immediately before use. ATP and adenosine were dissolved in physiologic saline, 20 mg/ml, solution. An ultrasonic vibrator (Bransonic 32) was used to facilitate dissolving adenosine.

Results

After a 60-minute period of stabilization under light halothane anesthesia, mean arterial blood pressure was 104 ± 6 torr and heart rate was 252 ± 7 beats per minute. Both adenosine and ATP caused a dose-related decrease in blood pressure and heart rate. The magnitude of the pressure effect peaked for ATP at a dose of 0.2 to 0.3 mg. With greater doses the duration of the hypotension increased as did the magnitude of bradycardia (Figs 1 and 2). The difference is related to the extremely short duration of action. Both ATP and adenosine reached their peak effects within 30 seconds (Table 1, Figs 1 to 3) and recovery was complete within 1 minute; sodium nitroprusside, by comparison, took almost twice as long to reach its peak effect and required 2 to 3 minutes for recovery (Table 1, Fig 3).

When the agents were given by continuous infusion for 30 minutes at a rate producing a similar magnitude of hypotension (approximately 45% decrease from control values) the onset of hypotension with all agents was rapid (Table 2). The effects of nitroprusside, however, became maximal somewhat more slowly, and thereafter there was a progressive recovery throughout the course of infusion (Fig 4). Adenosine and ATP, on the other hand, exerted immediate

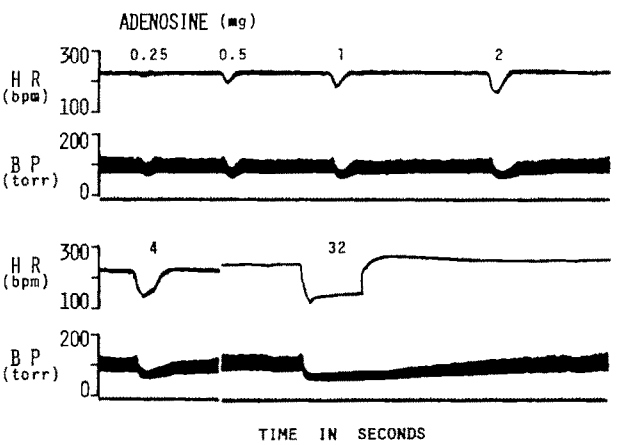


Fig 1. Effects of bolus intravenous injections of adenosine on blood pressure and heart rate. Increasing doses of adenosine were given as indicated. Note dose-dependent decrease of both blood pressure and heart rate. Abbreviations are: BP, arterial blood pressure (torr); HR, heart rate (beats/min).

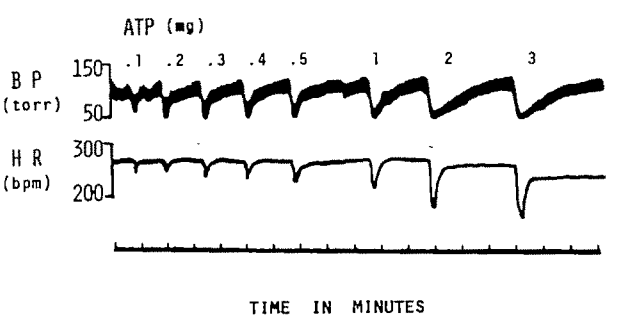


Fig 2. Effects of adenosine triphosphate (ATP) on blood pressure and heart rate. In this experiment sequentially increasing bolus doses of ATP were given as indicated. Note brevity of effects. Abbreviations as in Fig 1.

TABLE 1
Effects of Intravenous Bolus Injections*

	Dose	BP	HR	Onset	Recovery (80%)
	μg/kg	%		sec	
SNP (n = 13)	43 ± 9	−35 ± 3	5 ± 0	39 ± 3	153 ± 18
Adenosine (n = 13)	257 ± 36	−38 ± 3	−15 ± 3‡	22 ± 1‡	24 ± 4‡
ATP (n = 13)	257 ± 36	−41 ± 3†	−14 ± 3‡	24 ± 1‡	52 ± 9‡

* Values are means ± SEM. Abbreviations used are: BP, blood pressure; HR, heart rate; SNP, sodium nitroprusside; ATP, adenosine triphosphate.
† $p < 0.05$, paired t-test when compared with SNP.
‡ $p < 0.001$, paired t-test when compared with SNP.

TABLE 2
Effects of Intravenous Continuous Infusions*

	Dose	BP	HR	Onset	Recovery (80%)
	μg/kg/min	%		min	
SNP (n = 7)	24 ± 5	−43 ± 5	8 ± 1	2.8 ± 0.3	16 ± 1
Adenosine (n = 7)	984 ± 225	−45 ± 4	−11 ± 3†	2.1 ± 0.6	5 ± 1†
ATP (n = 7)	984 ± 225	−46 ± 3	−8 ± 2†	2.4 ± 0.8	5 ± 1†

* Values are means ± SEM. Abbreviations defined in footnote to Table 1.
† $p < 0.001$, paired t-test when compared with SNP.

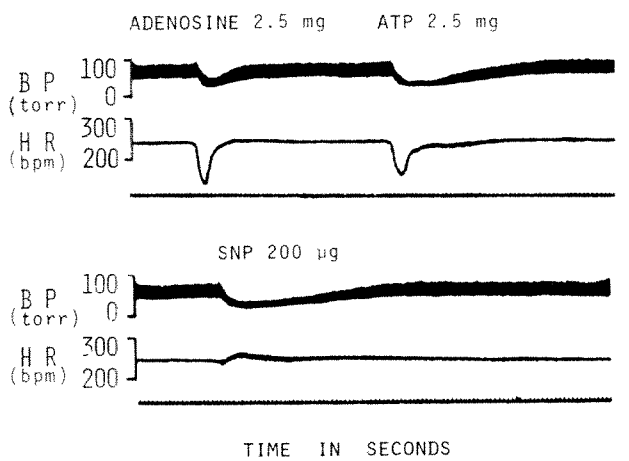


FIG 3. Comparison of effects of bolus injections of sodium nitroprusside (SNP) with those of adenosine and ATP. Notice differences in time course and in heart rate. Abbreviations as in Fig 1.

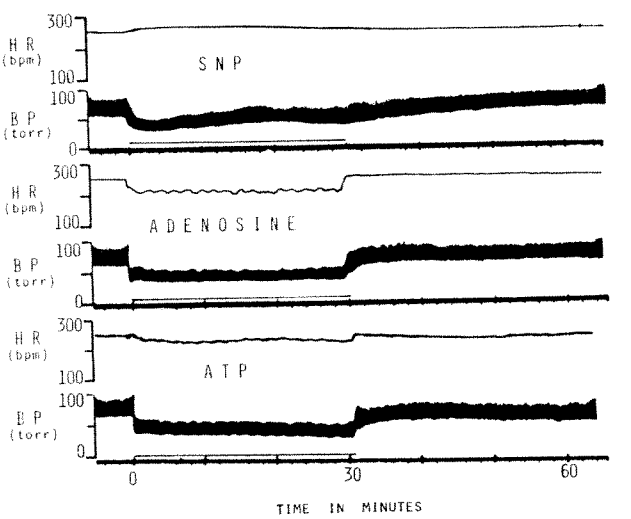


FIG 4. Hypotensive effects of SNP, adenosine, and ATP in rabbit anesthetized with halothane. Infusion of vasodilator is indicated by bar. Abbreviations as in Fig. 1. For details see "Methods."

hypotensive effects and blood pressure remained remarkably stable. No tachyphylactic responses were observed (Fig 4). On a weight basis, adenosine and ATP were almost equipotent, but the hypotension produced by ATP lasted slightly longer than that of adenosine. With bolus injections the adenine compounds were approximately 1/6 as potent as SNP (Table 1). The potency of adenine compounds when given as infusions was only 1/40 that of SNP (Table 2).

After termination of the infusion, blood pressure returned quickly to preinfusion levels with both adenosine and ATP (5 ± 1 minutes) (Table 2); there was no rebound hypertension. With SNP, however, although systolic pressure had returned to near control levels during continued infusion, another 20 to 30 minutes was required for blood pressure to recover completely after termination, and overshoot was frequent (Fig 4).

Another important difference between nitroprus-

side and the adenine compounds was the effect on the heart rate. Nitroprusside invariably increased heart rate with both bolus injection and with continuous infusion (Figs 3 and 4). In contrast, adenine compounds, when injected in bolus, caused a dose-dependent decrease in both heart rate and blood pressure (Figs 1 and 2). Continuous infusions of adenosine and ATP had small but statistically significant negative chronotropic effects (Fig 4, Table 2).

Discussion

Adenosine triphosphate is often considered almost exclusively in terms of its role in intracellular metabolism. However, it has long been known that purine nucleotides and nucleosides exert many extracellular actions on excitable membranes in various tissues (2, 3, 6). In fact, there is growing evidence that these compounds have important physiologic roles as mediators of nerve activity (5), in regulating transmitter release (6, 16–22), and as major factors in the local regulation of blood flow to tissues (4, 6, 23–25).

The actions of adenine compounds on the cardiovascular tissues are among their most striking extracellular actions. These effects involve not only the neurogenic and local control of blood flow but also direct actions on electrical and contractile properties of the heart (6, 26).

In view of this well established body of knowledge, it is perhaps surprising that these compounds have not been considered more seriously as hypotensive agents in recent years, when acute control of blood pressure became the subject of such great interest (7, 8). This is especially so in view of the well documented shortcomings of sodium nitroprusside and nitroglycerin, the drugs used most widely for this purpose. Nitroprusside-induced hypotension has frequently been reported to elicit general reflex sympathetic activation manifested as tachycardia and increase in contractility (9, 27–31) and as increases in levels of plasma renin and catecholamines (32) (Fukunaga AF, Bloor BC, Flacke WE. Plasma catecholamine levels and circulatory changes during I.V. infusion of ATP and sodium nitroprusside in dogs. Paper presented at the Eighth International Congress of Pharmacology, July 1981, Tokyo, Japan). These reflexly elicited changes may be responsible for the development of tachyphylaxis and postinfusion or "rebound" hypertension (33). When, because of tachyphylaxis, high doses of SNP are required, metabolic acidosis and cyanide toxicity may result (7, 34). Other undesirable effects of SNP have also been reported (35, 36). Hence, a search for a safer and more effective means for acute blood pressure control, especially one associated with no or lesser autonomic responses, is certainly indicated.

In the present studies heart rate was taken as the main indicator of baroreceptor reflex activity during hypotension. To a lesser extent, recovery during sustained infusion of the hypotensive drug and rebound hypertension were also interpreted as indicators of reflex activity. It was apparent that the adenine compounds elicited no reflex tachycardia as did SNP under identical conditions (Figs 1 to 4, Tables 1 and 2). No tachyphylaxis or rebound hypertension was seen with adenosine or ATP. These observations were made after a 60-minute stabilization period during light levels of halothane anesthesia. The magnitude of the hypotension studied was approximately 45% from control values, that is, a level resembling that required under clinical conditions for controlled hypotension.

The conclusions of the present investigation apply only to the conditions studied. Factors such as type and depth of anesthesia, magnitude and duration of hypotension, and fluid management may influence the changes that occur during hypotension, and these factors were not systematically investigated. However, in the more recent studies concerning induced hypotension with ATP (10–15) neither depth of anesthesia nor dose of ATP was clearly defined (dose was manually regulated by drip rate). The only well described study we have been able to find was that by Rowe and associates (37). Their study was performed in dogs after subcutaneous administration of 3 mg/kg of morphine supplemented by a mixture of pentobarbital and allobarbital (Dial)-urethane (doses not given). Under these conditions, infusion of adenosine or of ATP in doses similar to those that we used (2 μmol/kg/min) elicited a marked tachycardia of +65% and +72%, respectively, while decreasing blood pressure only 9% and 14%, respectively. It seems probable that differences in premedication and anesthesia in our study and in theirs may have been responsible for the differences in the responses of blood pressure and heart rate to infusions of adenosine and ATP.

The actions of both adenosine and ATP were rapid in onset and dissipated almost equally as rapidly after discontinuation of infusion. It is, of course, well known that ATP is rapidly degraded to adenosine by ecto-enzymes, ATPase, and 5-nucleotidase. Adenosine is taken up and further broken down by adenosine deaminase. Adenine is 10 to 20 times less potent a vasodilator than adenosine (25).

Thus, under the conditions of our experiments both

adenosine and ATP caused marked and well maintained hypotension without tachycardia, tachyphylaxis, or rebound hypertension. In this they compared favorably with sodium nitroprusside. The time course of the hypotensive action was very short, shorter by far than SNP, which is usually considered to be short-acting. This extremely rapid and brief hypotensive action can be considered an advantage or a disadvantage. Of course, for a hypotensive effect of any useful duration administration by continuous infusion with even and precise control is mandatory. With continuous observation, quick titration to the desired level of blood pressure without signs of reflex activation appears to be possible with infusions of either ATP or adenosine during halothane anesthesia. Excessive bradycardia, which was seen with higher bolus doses (Figs 1 and 2), was never observed when the agents were given by continuous infusion.

Although much information about the extracellular, especially cardiovascular, effects of the adenine nucleotides has been accumulated, clinical use will require more information in different species and under a variety of conditions. One question stands out: Why do the purine nucleotides elicit less baroreceptor reflex response than does SNP? The answer may well lie in the observations made some time ago by Emmelin and Feldberg (38) and Jarisch and Zotterman (39) that ATP stimulates afferent sensory receptors in heart and lung which reflexly inhibit autonomic efferent activity (40).

ACKNOWLEDGMENTS

Adenosine triphosphate-2Na (ATP) for these studies was donated by Kyowa Hakko Kogyo Co., Ltd. The authors thank Rose Antonucci for her expert secretarial assistance.

REFERENCES

1. Drury AN, Szent-Györgyi A. The physiological activity of adenine compounds with especial reference to their action upon the mammalian heart. J Physiol (Lond) 1929;68:213–37.
2. Green HN, Stoner HB. Biological actions of the adenine nucleotides. London: HK Lewis, 1950.
3. Boettge K, Jaeger KH, Mittenzwei H. Das Adenylsäuresystem. Arzneim Forsch 1957;7:24–59.
4. Berne RM. Cardiac nucleotides in hypoxia: possible role in regulation of coronary blood flow. Am J Physiol 163;204:317–22.
5. Burnstock G. Purinergic nerves. Pharmacol Rev 1972;24:509–81.
6. Baer HP, Drummond GI, eds. Physiological and regulatory functions of adenosine and adenine nucleotides. New York: Raven Press, 1979.
7. Tinker JH, Michenfelder JD. Sodium nitroprusside: pharmacology, toxicology and therapeutics. Anesthesiology 1976;45: 340–54.
8. Saito D, Ueda M, Yoshida H, et al. Comparative vasodilator effects of nitroprusside, phentolamine, and nitroglycerin on hemodynamics, regional myocardial function and epicardial electrogram in dogs with acute myocardial ischemia. Jpn Heart J 1978;19:926–37.
9. Flacke JW, Flacke WE, Cant JW. Reflex responses to sodium nitroprusside and their control by cryptenamine. Anesth Analg 1980;59:909–16.
10. Hatano S, Aso K, Hirose Y, Shikada K, Yonekura M, Fukuuchi K. Surgical application of adenosine triphosphate (ATP)—special reference to deliberate hypotension (in Japanese). Clin Surg 1959;14:859–63.
11. Tanaka R, Nakano Y, Watanabe S, et al. Study on deliberate hypotension with ATP (in Japanese). Jpn J Anesthesiol 1975;14: 1093–5.
12. Maruyama M, Sato K, Shimoji K. Hypotensive anesthesia using ATP (in Japanese). Jpn J Anesthesiol 1978;27:1533–40.
13. Numajiri Y, Mokuji T, Kagami K, Niki H, Yoshida K, Hosoyamada A. ATP induced hypotensive anesthesia during prosthetic hip surgery (in Japanese). J Clin Anesthesiol 1979;3:279–84.
14. Tanaka A, Mori H. Systemic hemodynamics during hypotension induced by sodium nitroprusside, ATP and halothane (in Japanese). Jpn J Anesthesiology 1977;26:739–46.
15. Maruno Y, Hashimoto Y, Saito N, Okazaki N, Fujii A, Aono M. The effects of 50% hypotension induced by ATP, sodium nitroprusside and trimethaphan on canine cerebral blood flow and metabolism (in Japanese). Jpn J Anesthesiology 1978;27: 1525–32.
16. Fredholm BB, Hedqvist P. Commentary: modulation of neurotransmission by purine nucleotides and nucleosides. Biochem Pharmacol 1980;29:1635–43.
17. Clanachan AS. Modification of release by adenosine and adenine nucleotides. In: Paton DM, ed. The release of catecholamines from adrenergic neurons. Oxford: Pergamon Press, 1979:263–73.
18. Westfall TC. Local regulation of adrenergic neurotransmission. Physiol Rev 1977;57:659–728.
19. Verhaeghe RH, Vanhoutte PM, Shepard JT. Inhibition of sympathetic neurotransmission in canine blood vessels by adenosine and adenine nucleotides. Circ Res 1977;40:208–15.
20. Clanachan AS, Johns A, Paton DM. Presynaptic inhibitory actions of adenine nucleotides and adenosine on neurotransmission in rat vas deferens. Neuroscience 1977;2:597–602.
21. Ginsborg BL, Hirst GIS. The effect of adenosine on the release of the transmitter from the phrenic nerve of the rat. J Physiol 1972;224:629–45.
22. Ribeiro JA, Walker J. The effects of adenosine triphosphate and adenosine diphosphate on transmission at the rat and frog neuromuscular junctions. Br J Pharmacol 1975;213–8.
23. Burnstock G. Purinergic receptors in the heart. Circ Res 1980;46SupplI:175–82.
24. Wolf MM, Berne RM. Coronary vasodilator properties of purine and pyrimidine derivatives. Circ Res 1956;4:343–8.
25. Paddle BM, Burnstock G. Release of ATP from perfused heart during coronary vasodilatation. Blood Vessels 1974;77:110–9.
26. Belardinelli L, Belloni FL, Rubio R, Bern RM. Atrioventricular conduction disturbances during hypoxia: possible role of adenosine in rabbit and guinea pig heart. Circ Res 1980;47:684–91.
27. Taylor TH, Styles M, Lamming AJ. Sodium nitroprusside as a hypotensive agent in general anaesthesia. Br J Anaesth 1970;42: 859–64.
28. Adams AP, Clark TNS, Edmonds-Seal J, Foëx P, Prys-Roberts C, Roberts JG. The effects of sodium nitroprusside on myocardial contractility and haemodynamics. Br J Anaesth 1974;46: 807–17.
29. Wildsmith JAW, Marshall RL, Jenkinson JL, MacRae WR, Scott DB. Haemodynamic effects of sodium nitroprusside during nitrous oxide/halothane anaesthesia. Br J Anaesth 1973;45: 71–4.
30. Pagan M, Vatner SF, Braunwald E. Hemodynamic effects of intravenous sodium nitroprusside in the conscious dog. Circulation 1978;57:144–51.

31. Fahmy NR, Roberts JT, Lappas DG. Nitroprusside-induced hypotension: role of heart rate in determining hemodynamic effects and tachyphylaxis. Anesthesiology 1979;51:S71.
32. Fahmy NR, Sunder N, Moss J, Slater E, Lappas DG. Tachyphylaxis to nitroprusside: role of the renin-angiotensin system and catecholamines in its development. Anesthesiology 1979;51:S72.
33. Packer M, Meller J, Medina N, Gorlin R, Herman MV. Rebound hemodynamic events after the abrupt withdrawal of nitroprusside in patients with severe chronic heart failure. N Engl J Med 1979;301:1193–7.
34. Grayling GW, Miller ED, Peach MJ. Sodium cyanide antagonism of the vasodilator action of sodium nitroprusside in the isolated rabbit aortic strip. Anesthesiology 1978;49:21–5.
35. Miller R, Stark DC. Correspondence: acute phlebitis from nitroprusside. Anesthesiology 1978;49:372.
36. Fahmy NR. Consumption of vitamin B-12 during sodium nitroprusside administration in humans. Anesthesiology 1981;56: 305–9.
37. Rowe GG, Alfonso S, Gurtner HP, et al. The systemic and coronary hemodynamic effects of adenosine triphosphate and adenosine. Am Heart J 1962;64:228–34.
38. Emmelin N, Feldberg W. Systemic effects of adenosine triphosphate. Br J Pharmacol 1948;3:273–84.
39. Jarisch A, Zotterman Y. Depressor reflexes from the heart. Acta Physiol Scand 1948;16:35–51.
40. Fukunaga AF, Miyamoto JK. Hypotensive action of adenine compounds. Anesthesiology 1980;53:S90.

Respiratory Failure Due to Cricoarytenoid Arthritis

A 69-year-old man with a 20-year history of ankylosing spondylitis involving the entire spine and sarcroiliac joints presented with a history of increasing breathlessness for two months and noisy breathing and hoarseness for one month. On admission, he was in respiratory distress with inspiratory stridor, expiratory rhonchi, and evidence of cor pulmonale. Indirect laryngoscopy revealed erythema and edema of the vocal cords with bilateral fixation in the paramedian position. Hypoxemia and respiratory acidosis necessitated endotracheal intubation, performed with the endotracheal tube "sleeved" over a bronchofiberscope. After two unsuccessful attempts at extubation direct fiberoptic laryngoscopy showed paramedian fixation of the vocal cords reducing the airway diameter to 1.5 to 2.0 mm. The patient underwent endoscopic right arytenoidectomy under general anesthesia which increased the airway diameter to approximately 6.0 mm. Flow-volume curves performed 2 weeks postoperatively documented extrathoracic airway obstruction produced by ankylosis of the cricoarytenoid joints. *(Libbey DM, Schley WS, Smith JP. Cricoarytenoid arthritis in ankylosing spondylitis: a cause of acute respiratory failure and cor pulmonale. Chest 1981;80:641–3)*

ANESTH ANALG
1982;61:279-83

Neurologic Effects of Subarachnoid Administration of 2-Chloroprocaine-CE, Bupivacaine, and Low pH Normal Saline in Dogs

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RAVINDRAN, R. S., TURNER, M. S., AND MULLER, J.: Neurologic effects of subarachnoid administration of 2-chloroprocaine-CE, bupivacaine, and low pH normal saline in dogs. Anesth Analg 1982;61:279-83.

The purpose of this study was to evaluate the neurologic consequences of deliberate subarachnoid injection of large volumes of 2-chloroprocaine-CE in experimental animals. The possible role of low pH as well as total volume as potential factors in causing neurotoxicity was evaluated. The 65 dogs in the study received injections in the subarachnoid space as follows: 6 to 8 ml of bupivacaine (N = 15), 2-chloroprocaine-CE (N = 20), low pH normal saline (pH 3.0) (N = 20), or normal saline (N = 10). Of the 20 animals that received subarachnoid injection of 2-chloroprocaine-CE seven (35%) developed hind-limb paralysis. None of the animals that received bupivacaine, normal saline, or normal saline titrated to a pH 3.0 developed hind-limb paralysis. Of the 15 spinal cords of the animals that received 2-chloroprocaine-CE, 13 showed subpial necrosis; the nerve roots and subarachnoid vessels were normal. The spinal cords of the animals that received bupivacaine, low pH normal saline (pH 3.0), or normal saline did not show abnormal findings.

Key Words: ANESTHETICS, Local: 2-chloroprocaine-CE, bupivacaine; TOXICITY: local anesthetics.

RAVINDRAN et al (1) and Reisner et al (2) independently reported four cases of neurologic deficits associated with use of 2-chloroprocaine-CE for epidural anesthesia. In two of the patients the chloroprocaine was inadvertently injected into the subarachnoid space. In their editorial comments on these cases, Covino et al (3) stated that such complications were more likely to follow inadvertent subarachnoid injection of a large volume of 2-chloroprocaine-CE. They also speculated that the low pH of 2-chloroprocaine-CE might account for these neurologic complications. Therefore, we undertook an animal study to evaluate the neurologic consequences of deliberate subarachnoid injection of large volumes of 2-chloroprocaine-CE in dogs. The pH as well as total volume were evaluated as potential factors in causing neurotoxicity.

Methods

Sixty-five female mongrel dogs (8 to 18 kg each) were studied. Following sedation with intravenous ketamine (10 to 15 mg/kg), percutaneous lumbar punctures were performed at L5-6 in less than three attempts utilizing a 20-gauge spinal needle. Then 6 to 8 ml (depending on the crown-rump length) of a local anesthetic solution or normal saline was injected. The dogs were randomly divided into four groups. Dogs in group 1 (N = 20) had subarachnoid injection of 3% 2-chloroprocaine-CE (pH 3.3), those in group 2 (N = 15) 0.75% bupivacaine (pH 5.4), those in group 3 (N = 10) preservative-free normal saline, and those in group 4 (N = 20) preservative-free normal saline titrated to a pH of 3.0 by the addition of hydrochloric acid. Following subarachnoid injection of the local anesthetics the dogs in groups 1 and 2 became apneic. The tracheas of these dogs were intubated and the animals were ventilated with 100% oxygen. Following subarachnoid injection of saline the dogs in groups 3 and 4 developed opisthotonos but not apnea. Femoral arterial pressure was monitored with an arterial catheter and maintained at normal levels (90 to 120 torr) in groups 1 and 2 with the administration of fluids and vasopressors. No significant alterations in blood pressure were noted following subarachnoid injection of saline in groups 3 and 4. Following resumption of adequate spontaneous ventilation the tracheal tubes were removed and the dogs were observed in the

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Received from the Departments of Anesthesiology, Neurosurgery, and Neuropathology, Indiana University School of Medicine, Indianapolis, Indiana. Accepted for publication November 17, 1981.
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chronic animal care facility under the supervision and care of a veterinarian. All dogs from group 1 were killed 2 weeks after the subarachnoid injection. As the dogs from other groups clinically appeared to be normal, only a few representative dogs from other groups were randomly killed. The spinal cords were removed from these animals and multiple sections were taken following fixation in formalin. The sections were examined by the neuropathologist (J.M.) who was unaware of what had been injected into the subarachnoid space.

Results

With regression of anesthesia, 13 of 20 dogs in group 1 and all the dogs in groups 2 to 4 walked unassisted within 12 hours. Seven dogs in group 1 developed paralysis of the hind limbs. The paralyzed dogs showed no response to hind-limb pin-prick stimulation. These dogs also had bladder and bowel incontinence as evidence of lumbosacral cord involvement. Two of these dogs died spontaneously (6 and 8 days following study) and on autopsy (2 days after death) the spinal cords showed gross autolytic changes. In the other five dogs in group 1 neurologic changes persisted until the animals were killed 2 weeks later. One dog in group 2 and one dog in group 4 showed persistent limping of one of the hind limbs. Spinal cords removed from three dogs that had received chloroprocaine but were not paralyzed could not be examined because of poor fixation.

Multiple sections of the spinal cord taken at sacral, lumbar, and thoracic levels were examined. Sections taken from the five paralyzed and eight unparalyzed dogs that received 2-chloroprocaine-CE showed mild leptomeningitis and necrosis of the subpial area of the cord in the lumbar area. Minimal inflammatory cellular infiltrate was noted in the periphery of the cord (Figs 1 and 2). The nerve roots, in contrast, showed no significant changes (Figs 1 and 3). Despite close scrutiny, no vascular pathology was observed. The changes were more marked and more circumferential in the paralyzed dogs. Sections of the sacral segment of the cord showed minimal leptomeningeal cellular infiltration. Sections of the thoracic segment of the cord were normal. Sections of the spinal cords of two unparalyzed dogs showed mild leptomeningeal infiltration. No subpial necrosis was noted (Fig 4).

In the dogs given bupivacaine whose cords were examined at autopsy (N = 4) the only finding was minimal leptomeningeal infiltration in the lumbar area (Fig 5). The one dog in this group that had limping following spinal anesthesia had traumatic injury (needle track) of the cord.

Sections of the thoracic, lumbar, and sacral seg-

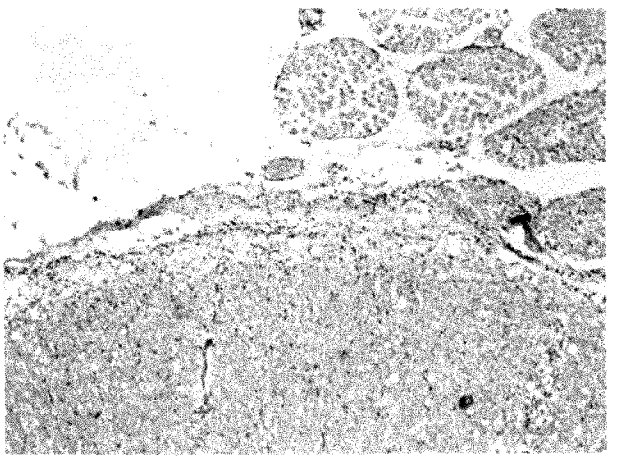


FIG 1. Subpial destructive zone contrasts with intact nerve rootlets above. Hematoxylin-eosin; 100×.

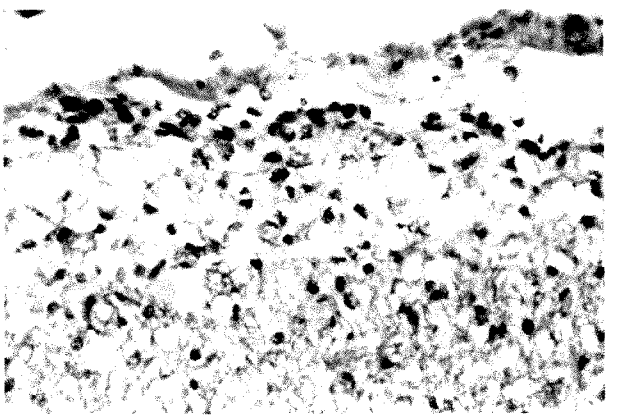


FIG 2. Extensive subpial destruction. Hematoxylin-eosin; 400×.

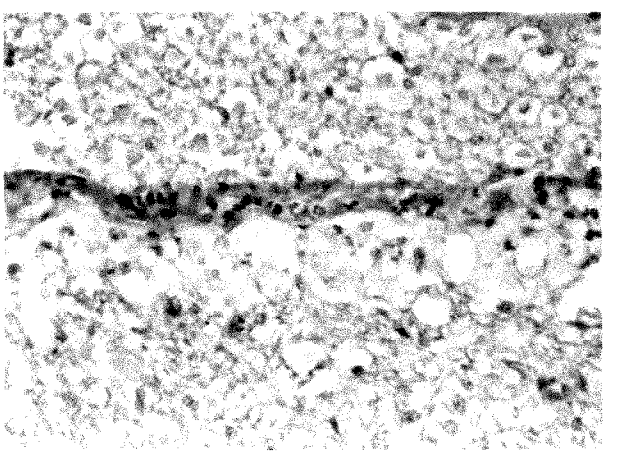


FIG 3. Subpial destruction, overlying nerve rootlet intact. Hematoxylin-eosin; 400×.

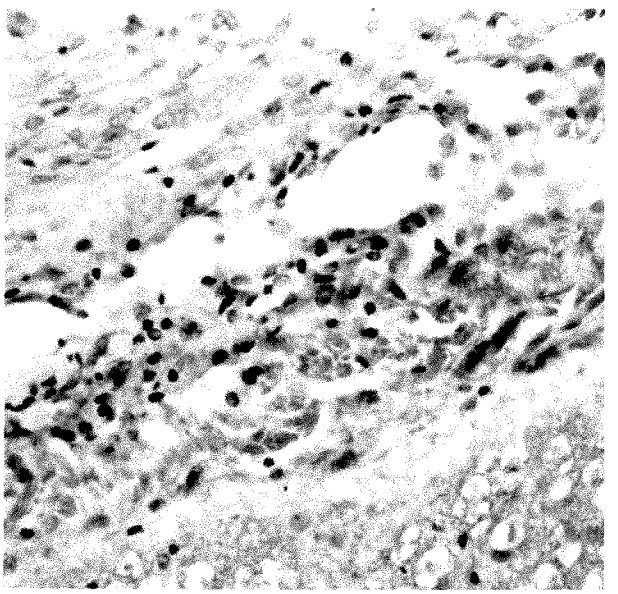


FIG 4. Subpial inflammatory infiltrate, intact nerve root above. Hematoxylin-eosin; 400×.

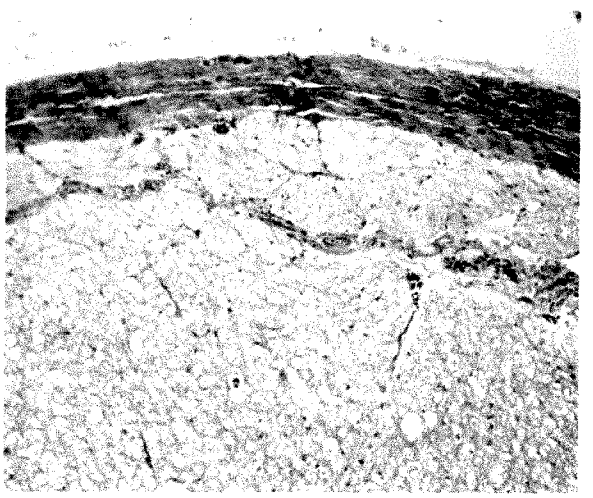


FIG 5. Normal spinal cord and nerve root. Hematoxylin-eosin; 100×.

ments of the spinal cord of two dogs from groups 3 and 4 were normal. The dog from group 4 that had limping of one of the hind limbs also had needle injury to the cord.

Discussion

2-Chloroprocaine hydrochloride was introduced as a local anesthetic for clinical use in 1952. At that time it was marketed as a colorless crystal in 10- and 20-ml vials (100 and 400 mg). Foldes and McNall (4) reported the initial clinical evaluation of the drug for regional anesthesia, including spinal anesthesia, in a large number of patients without any adverse effects. In 1956, the trade name of 2-chloroprocaine was changed from Helestyn to Nesacaine. In the 1960s additives and preservatives were included to increase the shelf-life of the solution. In the 1970s two preparations of 2-chloroprocaine were available: one with preservative for local infiltration anesthesia, the other, 2-chloroprocaine-CE, without preservative (but with sodium bisulfite) for use in caudal and epidural anesthesia. In the late 1970s the technique of continuous lumbar epidural analgesia to provide pain relief during labor and delivery became popular because (*a*) more anesthesiologists became interested in the field of obstetric anesthesia, (*b*) better epidural catheters were available, and (*c*) the safety of lumbar epidural analgesia for labor and delivery by then had become well established. Because of its several unique properties including rapid onset, short duration, and few maternal and fetal effects due to its rapid hydrolysis by pseudocholinesterase, 2-chloroprocaine-CE became a popular anesthetic for use in obstetric anesthesia.

Thousands of epidural anesthesias were performed with 2-chloroprocaine-CE between 1977 and 1980 without any reported cases of neurologic complications. However, in 1980 Ravindran et al (1) reported that two of their patients who had received continuous epidural anesthesia with 2-chloroprocaine-CE developed prolonged neurologic dysfunction. In these two patients the rapid onset of perineal anesthesia suggested the possibility that some of the drug might have entered the subarachnoid space. At the same time, Reisner et al (2) and Ravindran et al (1) independently reported neurologic dysfunction in two of their patients in one of whom there was documented evidence of inadvertent subarachnoid injection of 2-chloroprocaine-CE. Occurrences of four cases of prolonged neurologic dysfunctions following epidural and inadvertent subarachnoid injection of 2-chloroprocaine-CE within a few years became a matter of serious concern to anesthesiologists. The Pennwalt Corporation (maker of 2-chloroprocaine-CE) organized a symposium to discuss the problem of neurotoxicity associated with the use of 2-chloroprocaine-CE. Following that symposium, Covino et al (3) in their editorial comments stated that neurologic dysfunctions might follow inadvertent subarachnoid injection of a large volume of 2-chloroprocaine-CE and offered recommendations to prevent, recognize, and treat such rare occurrences. Although 2-chloroprocaine-CE is not recommended for subarachnoid injection, such an incident could occur during epidural

anesthesia even following a negative test dose or top up dose (5, 6). In fact, one of the proposed mechanisms of action of epidural anesthesia is by the entry of the local anesthetic into the subarachnoid space (7). Therefore, any epidural medication should not produce any adverse reaction in the subarachnoid space. There have been at least two published reports of inadvertent subarachnoid injection of 2-chloroprocaine-CE unassociated with the development of neurologic dysfunctions (5, 6). Perhaps there might have been unreported instances of inadvertent subarachnoid injection of 2-chloroprocaine-CE unassociated with any neurologic dysfunction. Nevertheless, the recent occurrences of several reported and unreported cases of neurologic dysfunctions following inadvertent subarachnoid injection of 2-chloroprocaine-CE necessitate a review and evaluation of the neurotoxicity of this drug in various types of blocks.

Piro et al (8) noted that submucosal injection of 2-chloroprocaine produced no gross or histopathologic changes. 2-chloroprocaine has been successfully used for epidural anesthesia (9) and regional blocks (10). Foldes and McNall (4) administered spinal anesthesia to a large number of patients with 2-chloroprocaine without any adverse effects. However, the 2-chloroprocaine they used had different physicochemical properties than the currently available 2-chloroprocaine-CE (11). Barsa et al (12) noted that in rabbits perineural injection of 2-chloroprocaine-CE resulted in the development of perineural adhesions, axonal degeneration, and impaired conduction along the treated nerves. However, in another study utilizing the same experimental model as Barsa et al (12) similar histopathologic changes in lidocaine-treated rabbit vagus nerves were noted as well (Riggi SJ, Harding S, Hashim M, Hinsvark O. The toxicity of 2-chloroprocaine and lidocaine on peripheral nerves of rabbits. Abstracts of scientific papers, Annual Meeting of Society for Obstetric Anesthesia and Perinatology, April 1981, San Diego, California). They, however, did not do conduction studies on those nerves. The study also noted that peribrachial plexus injection of 2-chloroprocaine-CE did not produce histopathologic changes.

In our study we decided to use 6 ml or more of a local anesthetic as it was the amount required to induce diaphragmatic paralysis in most of the dogs and also it would be the amount analogous to the clinical situation in man wherein inadvertent injection of 20 to 25 ml would almost replace the spinal cerebrospinal fluid (35 ml) (13).

The development of apnea immediately following the injection of a local anesthetic showed that the drugs were, in fact, injected into the subarachnoid space of the dogs. Of the 20 dogs that received subarachnoid injection of 2-chloroprocaine-CE seven developed permanent neurologic dysfunctions, whereas none of the dogs that received subarachnoid injection of similar volumes of bupivacaine developed neurologic dysfunctions (except for the dog that had trauma to the cord). The fact that the histopathologic changes in the affected dogs were confined to the subpial area of the spinal cord close to the site of injection suggests the possibility of a neurotoxic effect involving primarily the surface of spinal cord. The adverse effects could not have been caused by trauma during the performance of lumbar puncture; in the few dogs in which needling injury was noted the lesions were quite different from the ones noted in the paralyzed dogs. Confinement of the lesion only to the subpial area of the cord also rules out a vascular etiology. In addition, sections of the spinal cord that had spinal vessels were noted to be normal. In this study, the spinal cords of the animals that received large volumes of bupivacaine or saline did not show subpial necrosis.

2-Chloroprocaine-CE is unique among local anesthetics in having a low pH (pH 2.7 to 4.2). Could the low pH of the drug have caused the histopathologic changes noted in the spinal cords of the affected animals? The dogs that received the low pH saline (pH 3.0) had neither neurologic dysfunction nor histopathologic changes. Lundy et al (14) noted in dogs that subarachnoid injection of 10 ml of saline or of 5 ml of hyperosmotic solutions such as 40% dextrose, 18.5% urea, or 10 ml of 12.5% procaine did not produce any adverse effects. However, subarachnoid injection of 5 ml of 20% procaine produced hind limb paralysis in all the animals. The spinal cords of those animals showed subpial necrosis. The spinal roots and the blood vessels were normal. Feldman and Covino (15) noted in dogs that subarachnoid injection of 1 ml of 3% 2-chloroprocaine-CE did not produce any neurologic dysfunctions. Clinical experience has shown that subarachnoid injection of small amounts of 2-chloroprocaine does not produce any adverse effect (4). However, another study noted that in sheep subarachnoid injection of a large volume of 2-chloroprocaine-CE or sodium bisulfite (an antioxidant present in 2-chloroprocaine-CE) did not produce any adverse clinical effects or histopathologic changes (Rosen MA, Norton M, Curbis JD, et al. Evaluation of local anesthetics for neurotoxicity following subarachnoid injection. Abstracts of scientific papers,

Annual Meeting of Society for Obstetric Anesthesia and Perinatology, April 1981, San Diego, California). What is unique about the pharmacokinetics of 2-chloroprocaine-CE in the cerebrospinal fluid? The subarachnoid space of the dog like that in man is almost devoid of pseudocholinesterase (measured in our laboratory). Injection of large volumes of 2-chloroprocaine-CE (pH 2.7 to 4.2) (16) could significantly decrease the pH of spinal cerebrospinal fluid. At a pH less than 6.0 almost no alkaline hydrolysis occurs. A significant proportion of 2-chloroprocaine-CE (pKa 8.7) will remain in ionized form in acidic solutions (17). Therefore, it is possible that subarachnoid injection of a large amount of 2-chloroprocaine-CE might result in its remaining in the subarachnoid space for a long time and producing a surface effect. However, we are puzzled by the fact that such effects were not noted by other investigators studying sheep.

In conclusion, subarachnoid injection of 2-chloroprocaine-CE in dogs resulted in the development of neurologic dysfunction in 35% of the animals studied. The histologic findings in the paralyzed animals were restricted to superficial areas of subarachnoid tissues. Similar changes were not noted in the dogs given subarachnoid injections of bupivacaine, saline, or saline titrated to a pH of 3.0. In evaluating the results of this study one should consider the possibility that the response noted in dogs in the subarachnoid injection of 2-chloroprocaine-CE might be different from that associated with the subarachnoid injection of the drug in other animals or in man.

ACKNOWLEDGMENT

The authors thank Dr. Robert K. Stoelting, Professor and Chairman, Department of Anesthesia, Indiana University School of Medicine, for his helpful suggestions in the preparation of this paper.

REFERENCES

1. Ravindran RS, Bond VK, Tasch M, Gupta CD, Leurssen TG. Prolonged neural blockade following regional analgesia with 2-chloroprocaine. Anesth Analg 1980;59:446–51.
2. Reisner LS, Hochman BN, Plumer MH. Persistent neurologic deficit and adhesive arachnoiditis following intrathecal 2-chloroprocaine injection. Anesth Analg 1980;59:452–4.
3. Covino BG, Marx GF, Finster M, Zsigmond ED. Prolonged sensory/motor deficits following inadvertent spinal anesthesia. Anesth Analg 1980;59:399–400.
4. Foldes FF, McNall PG. 2-Chloroprocaine, a new local anesthetic agent. Anesthesiology 1952;13:287–96.
5. Allen PR, Johnson RW. Subarachnoid injection during extradural analgesia for labour using 2-chloroprocaine. Anaesthesia 1979;34:874–6.
6. Kim YI, Mazza NM, Marx GF. Massive spinal block with hemicranial palsy after a "test dose" for extradural analgesia. Anesthesiology 1975;43:370–2.
7. Usubiaga JE, Wikinski J, Wikinski R. Transfer of local anesthetic to the subarachnoid space and mechanisms of epidural block. Anesthesiology 1964;25:752–9.
8. Piro JD, Sproul EE, Zegarelli EV, Katscher AH. Effects of Cyclaine,[R] Bonocaine,[R] Xylocaine[R] and Oracaine[R] on the oral mucous membranes. Anesth Analg 1954;33:391–4.
9. Colavincenzo JW, Foldes FF, McNall PG. The use of 2-chloroprocaine hydrochloride for epidural block in outpatients. Pa Med J 1956;59:338–40.
10. Harris WH, Slater EM, Bell HM. Regional anesthesia by the intravenous route. JAMA 1965;194:1273–6.
11. Friedman G, DiFazio C. Prolonged neural blockade following regional analgesia with 2-chloroprocaine. Anesth Analg 1980;59:810.
12. Barsa JE, Batra M, Fink RB. Prolonged neural blockade following regional analgesia with 2-chloroprocaine. Anesth Analg 1980;59:810–1.
13. Lund PC. Principles and practice of spinal anesthesia. Springfield, IL: Charles C Thomas, 1971:72.
14. Lundy JS, Essex HE, Kernohan JW. Experiments with anesthetics. JAMA 1933;10:1546–50.
15. Feldman HS, Covino BG. A chronic model for investigation of experimental spinal anesthesia in the dog. Anesthesiology 1981;45:148–52.
16. Nesacaine[R] (chloroprocaine hydrochloride) product monograph. Rochester, NY: Pennwalt Pharmaceutical Division.
17. Covino BG, Vassallo HG. Local anesthetics: mechanisms of action and clinical use. New York: Grune & Stratton, 1976:46.

ANESTH ANALG
1982;61:284-7

Inaccuracy of Liquid Crystal Thermometry to Identify Core Temperature Trends in Postoperative Adults

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VAUGHAN, M. S., CORK, R. C., AND VAUGHAN, R. W.: Inaccuracy of liquid crystal thermometry to identify core temperature trends in postoperative adults. Anesth Analg 1982;61:284-7.

In 71 adult postsurgical patients, simultaneous measurement of core (tympanic membrane) and shell (liquid crystal adhesive temperature strip) cutaneous temperature was assessed on admission and every 15 minutes throughout the recovery room stay. Tympanic membrane sensors were inserted into the ear and adhesive temperature strips were applied to the forehead. Although temperature strip temperatures on admission to the recovery room were correlated significantly with tympanic membrane temperatures on admission to the recovery room ($r = 0.61$, $p < 0.001$), subsequent readings 15, 30, 45, and 60 minutes after admission demonstrated decreasing correlation coefficients. Moreover, changes in temperature strip temperatures over the first 15, 30, and 45 minutes of monitoring in the recovery room did not correlate significantly with changes in tympanic membrane temperatures over the same time period. These data suggest that shell temperature (temperature strip) is not a reliable or valid trend indicator of core temperature (tympanic membrane) in postanesthetic adults.

Key Words: TEMPERATURE: body; MONITORING: temperature; MEASUREMENT TECHNIQUES: liquid crystal thermometry.

TEMPERATURE aberrance, either hypothermia or hyperthermia, can represent a significant risk for the patient undergoing anesthesia. Moreover, malignant hyperthermia has become a well publicized risk of anesthesia (1). However, incidental hypothermia during surgery and anesthesia, with its associated risks, occurs much more commonly. For example, hypothermia can produce delayed drug excretion and shivering with increased oxygen consumption, and it can potentiate cardiac dysrhythmias (2-4).

Studies to define and quantitate the risk of hypothermia and hyperthermia have used core temperature measurement as an index to assess thermal status of patients. Recently, another temperature monitoring development has been introduced into clinical practice. Commercially available Mylar strips that are impregnated with microencapsulated cholesteric liquid crystals have been designed for convenient placement (forehead) on the patient's skin. One brand, the Temp-A-Strip [Jelco Laboratories, Raritan, NJ (TS)], has been suggested for following patient temperatures during and after surgery (5, 6).

A majority of patients admitted to the recovery room (RR) after anesthesia and surgery tend to be hypothermic (7). Moreover, they are prone to peripheral vasoconstriction if the residual anesthetic is not interfering with heat regulatory functions. The application of a shell temperature monitor (TS) to the skin in such a circumstance becomes suspect as an accurate assessment of actual core temperature. The purpose of the present study was to determine whether these liquid crystal strips could be used in the RR as a reliable index of core body temperatures (i.e., trend indicator) in adult postsurgical patients.

Methods

After approval of the study protocol by the institutional Human Subjects Committee, oral and written consent was obtained from patients scheduled for surgery and subsequent monitoring in the RR. Excluded from the sample were patients (*a*) less than 17 years of age, and (*b*) those having open heart, intracranial, or middle ear operations. When a subject was admitted to the RR from the operating room, the same investigator (M.S.V.) inserted a disposable tympanic membrane (TM) sensor in either the left or right ear

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Received from the Departments of Pharmacology and Anesthesiology, University of Arizona Health Sciences Center, Tucson Arizona. Accepted for publication October 13, 1981. Presented in part at the Annual Meeting of the American Society of Anesthesiologists, October 12-16, 1980, St. Louis, Missouri.

following a random preassigned schedule and applied a liquid crystal adhesive strip (Temp-A-Strip) to the patient's forehead. The disposable TM sensor was inserted in a rotating motion after inspection of the ear canal, and gently advanced until resistance was encountered. The connecting monitoring unit (Mon-a-therm, LaBarge, Inc, St. Louis, MO) was calibrated before TM sensor insertion and before each clinical reading. The temperature sensing adhesive strip was applied parallel to and midway between the brow and hairline on the patient's clean, dry forehead. Admission temperature (within 5 minutes) and subsequent simultaneous readings were recorded every 15 minutes for each patient until discharge from the RR. Liquid crystal temperatures were interpreted according to the reference chart supplied and intermediate temperatures in 0.5°F increments were interpolated by comparison of the observed color. In all cases, the most brightly illuminated numerals were read. TM temperatures were measured in degrees Centigrade to the nearest 0.2°C, whereas TS temperatures were measured in degrees Fahrenheit to the nearest 0.5°F. The same observer (M.S.V.) read all liquid crystal temperatures and was not blind to the TM measurements. Data were analyzed using linear regression analysis and Student's t-test for paired data. Statistical significance was defined as $p < 0.05$.

Results

The study sample consisted of 71 patients, 37 men and 34 women. Sixteen patients had regional anesthesia whereas 55 patients received general anesthesia. Descriptive variables included [mean ± SE (range)]: age, 49.6 ± 2.2 years (17 to 83); weight, 72.2 ± 2.1 kg (40 to 132); height, 167.7 ± 1.5 cm (121 to 190); body surface area (BSA), 1.80 ± 0.03 m^2 (1.2 to 2.5).

Patient temperatures measured by the TM probe and the Temp-A-Strip are presented in Fig 1. Temperatures on admission to the RR measured 35.6 ± 0.1°C with the TM and 32.4 ± 0.1°C with the liquid crystal sensor (mean difference = 3.2°C, $p < 0.001$). Temperatures on discharge from the RR were 36.3 ± 0.1°C for TM and 33.6 ± 0.1°C for TS (mean difference = 2.7°C, $p < 0.001$).

Fig 2 shows the relationship between temperature measured by the TM and temperature measured by the TS on admission to the RR. A Centigrade conversion scale is provided for the TS measurements. Admission temperature measured by the liquid crystal thermometer correlated significantly with admission temperature measured with the TM ($r = 0.61$, $p < 0.001$). Table 1 shows subsequent readings after 15,

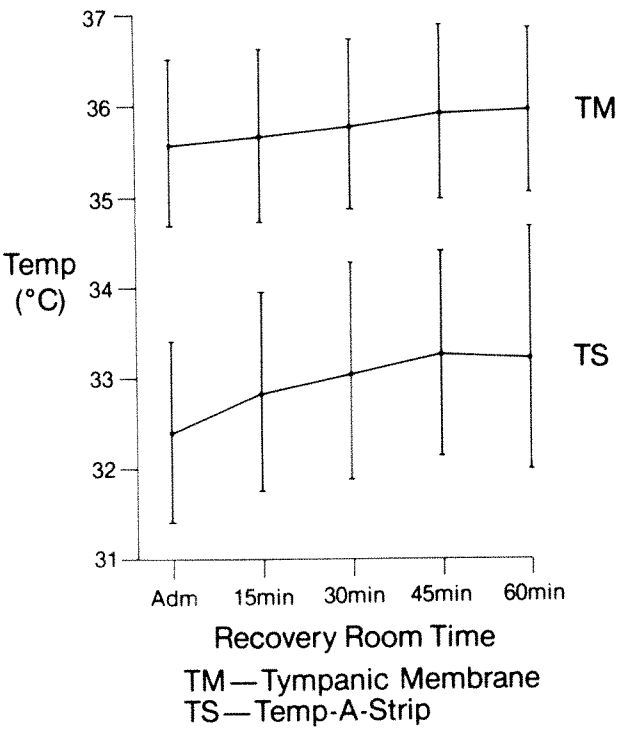


FIG 1. Tympanic membrane (TM) and shell [liquid crystal adhesive strip (TS)] temperature measurements taken simultaneously from admission to discharge in recovery room in 71 postsurgical adults. Values are means ± SD.

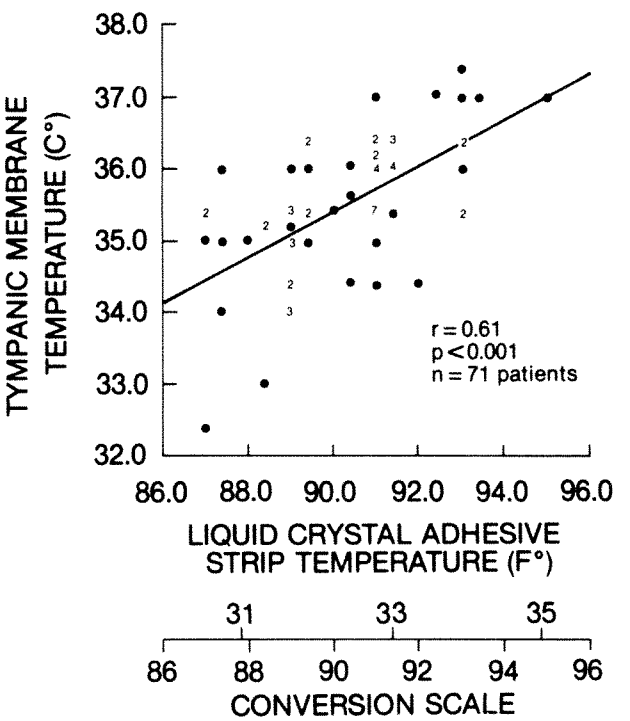


FIG 2. Core [tympanic membrane (TM)] and shell [liquid crystal adhesive strip (TS)] temperature measurements taken on admission to recovery room from 71 postsurgical adults. Each number in scattergram represents number of points at that locus.

30, 45, and 60 minutes as the effects of anesthesia dissipated. Although a statistically significant correlation exists between the two measurement methods, there is a progressive decrease in correlation coefficients (r) at each time point.

To examine the validity of liquid crystal thermometry as a trend indicator, the relationship between change in TS temperature and change in TM temperature was determined (Table 2). Five periods of time were examined for trends. All periods began at RR admission time. Temperature increase or decrease as observed with the TS thermometer was compared with increase or decrease in observed TM temperature over the same time period. Change in TS temperatures over the first 15, 30, and 45 minutes of the RR monitoring was not correlated significantly with change in TM temperatures over the same time periods. After 60 minutes of monitoring in the RR, the change in TS temperature correlated significantly with change in TM temperature ($p = 0.003$) but with a low correlation coefficient ($r = 0.36$). Overall change in TS temperature for the duration of stay in the RR was correlated significantly with change in TM temperature ($r = 0.47$, $p < 0.001$).

TABLE 1

Liquid Crystal Thermometer Temperature (TS) Compared with Tympanic Membrane Temperature (TM)

Recovery room time	TS range	TM range	Correlation coefficient (r)
min	°F	°C	
0	87.0–95.0	32.5–37.5	0.61
15	85.5–95.0	33.0–37.5	0.54
30	85.0–96.0	33.0–37.5	0.52
45	85.0–96.5	33.2–38.0	0.42
60	85.0–96.0	33.5–38.0	0.41
Discharge	87.0–96.5	33.5–38.0	0.39

TABLE 2

Change in Liquid Crystal Thermometer Temperature (ΔTS) Compared with Change in Tympanic Membrane Temperature (ΔTM) in Recovery Room

Recovery room time period	ΔTS* range	ΔTM* range	Correlation coefficient (r)	Significance (p)
min	°F	°C		
0–15	−2.5–4.0	−1.0–1.3	0.04	0.361
0–30	−4.0–4.0	−0.8–1.8	0.11	0.193
0–45	−4.0–6.0	−0.5–2.0	0.25	0.064
0–60	−4.0–5.0	−0.5–2.0	0.36	0.003
0–discharge	−2.0–6.0	−0.5–2.5	0.47	0.001

* Negative temperature changes indicate temperature decrease.

Discussion

The present study shows that TS correlates with TM at all measured times (Table 1). However, change as a function of time correlated only at 60 minutes (Table 2). Thus, TS appears to be inadequate for measuring trends in core temperature. When simultaneous slopes of TM and TS are compared in RR patients (Table 2), no significant correlation exists for the crucial initial 15, 30, or 45 minutes of RR stay. Perhaps this represents the multitude of postoperative variables that could affect peripheral circulation and thereby shell temperature. The resultant balance between heat supplied by the core circulation and the cooling of skin by radiation, convection, conduction, and evaporation could not be expected to predict concomitant changes in core temperature.

Previous studies (5, 6) have been presented to support liquid crystal adhesive strip monitoring of shell temperature during surgery as a trend indicator of core temperature. In six male patients undergoing therapeutic systemic hyperthermia, Lees et al (6) compared shell and core temperature recorded every 5 minutes for 2 hours. These data were combined to produce 46 data points for linear regression. However, linear regression requires independence of observation; otherwise, the analysis is invalid. Similarly, Burgess et al (5) implied that skin temperature assessment functions as a trend indicator, but supporting data were not presented.

In a series of experiments Benzinger (8) has shown that TM temperature is an accurate and precise indicator of core temperature. Gilston (9) reached the conclusion that nasopharyngeal temperature in patients anesthetized for cardiac surgery most closely reflects actual brain temperature. In addition, Hammel et al (10) have shown a reasonable correlation between hypothalamic and rectal temperatures. However, nasopharyngeal, esophageal, and rectal temperature sites are cumbersome and poorly tolerated by the awakening postanesthetic patient. TM monitoring, although convenient and reliable, is not without potential problems (11). However, to avoid complications Wallace et al (11) suggest otoscopic inspection of the canal and tympanic membrane before probe insertion, extreme care to stop insertion when resistance is met, and care to avoid sensor movement after probe placement.

In conclusion, the search continues for a noninvasive method to monitor core body temperature. Sim-

plicity and safety combined with instrument reliability and validity would characterize such a device. The clinician cannot embrace the former two characteristics without addressing the latter prerequisites of instrument reliability and validity. Finally, the question of whether liquid crystal thermometry may be useful in clinical situations to diagnose or follow trends with extreme temperature change (e.g., malignant hyperthermia) remains unanswered.

REFERENCES

1. Britt BA. Malignant hyperthemia: a pharmacogenetic disease of skeletal and cardiac muscles. N Engl J Med 1974;290:1140-2.
2. Bay J, Nunn JF, Prys-Roberts C. Factors influencing arterial PO_2 during recovery from anaesthesia. Br J Anaesth 1968;40: 398-406.
3. Dyson RD. Cell biology: a molecular approach. 2nd ed. Boston: Allyn and Bacon, 1978;46-66; 134-70; 461.
4. Hershey SG. General principals and determinants of circulatory transport. Anesthesiology 1974;41:116-23.
5. Burgess GE, Cooper JR, Marino RJ, Peuler, MJ. Continuous monitoring of skin temperature using a liquid crystal thermometer during anesthesia. South Med J 1978;70:516-8.
6. Lees DE, Schuette W, Bull JM, Wang-Peng J, Atkinson ER, Macnamara TE. An evaluation of liquid-crystal thermometry as a screening device for intraoperative hyperthermia. Anesth Analg 1978;57:669-74.
7. Vaughan MS, Vaughan RW, Cork RC. Postoperative hypothermia in adults: relationship of age, anesthesia, and shivering to rewarming. Anesth Analg 1981;60:746-51.
8. Benzinger TH. Clinical temperature: new physiological basis. JAMA 1969;209:1200-6.
9. Gilston A. Anaesthesia for cardiac surgery. Br J Anaesth 1971;43:217-32.
10. Hammel HT, Jackson DC, Stolwijk JAJ, Hardy JD, Stromme SB. Temperature regulation by hypothalamic proportional control with an adjustable set point. J Appl Physiol 1963;18:1146-54.
11. Wallace CT, Marks WE, Adkins WY, Mahaffey JE. Perforation of the tympanic membrane, a complication of tympanic thermometry during anesthesia. Anesthesiology 1974;41:290-1.

Epidemiology and Clinical Features of Anaphylactic Reactions in Anesthesia

Severe anaphylactoid reactions during anesthesia in 116 patients are described. The majority of patients who reacted to induction agents had previous exposure to the drug, whereas the majority of patients who reacted to muscle relaxants had not. There was a statistically significant increased incidence of allergy, atopy, asthma, and previous reactions in patients who had reactions compared with a control group undergoing uneventful anesthesia. There was no correlation between abnormalities in immunoglobulins or resting complement levels and a history of allergy or atopy. Antihistamines, steroids, and bronchodilators alone did not prevent reactions and three patients reacted to test doses with Althesin. Reactions usually occurred during induction of anesthesia, but may occur at any time in the perioperative period. No one drug produced reactions that differed in severity or clinical features from those of any other drug. Clinical features included skin changes, edema, cardiovascular collapse, bronchospasm, gastrointestinal symptoms, prolonged unconsciousness, convulsions, and pulmonary edema. Four patients died. Anaphylactoid reactions must be considered in the diagnosis of untoward events during anesthesia and adequate investigation undertaken to determine the cause of the event and the drug responsible. *(Fisher MMcD, More DG. The epidemiology and clinical features of anaphylactic reactions in anaesthesia. Anaesth Intensive Care 1981;9:226-34)*

ANESTH ANALG
1982;61:288-92

Antacid Aspiration in Rabbits: A Comparison of Mylanta and Bicitra

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EYLER, S. W., CULLEN, B. F., MURPHY, M. E., AND WELCH, W. D.: Antacid aspiration in rabbits: a comparison of Mylanta and Bicitra. Anesth Analg 1982;61:288-92.

The effects of aspiration of (*a*) 2 ml of Mylanta (a particulate antacid) mixed with 2 ml of hydrochloric acid (pH 1.5), (*b*) 2 ml of half-strength Bicitra (a soluble antacid) mixed with 2 ml of hydrochloric acid (pH 1.5), (*c*) 4 ml of hydrochloric acid (pH 1.5), and (*d*) 4 ml of normal saline (pH 6.5) on arterial blood gas tensions and lung pathology were compared in anesthetized rabbits. Pa_{O_2} decreased similarly in all animals 15 minutes after aspiration, but recovered to normal levels 4 hours after aspiration of saline and 48 hours after aspiration of Bicitra. Pa_{O_2} remained depressed after aspiration of Mylanta and HCl. Gross and microscopic evidence of lung injury was most severe in animals that aspirated Mylanta. One animal died 8 hours after aspiration of Mylanta.

Key Words: LUNG: aspiration; COMPLICATIONS: aspiration.

THE DANGERS of acid aspiration have been recognized since Mendelson's classic paper published in 1949 (1). Administration of oral antacids to parturients before induction of anesthesia has been recommended in order to reduce the risk of chemical pneumonitis should aspiration occur (2). However, aspiration of neutral gastric contents containing small foodstuff particles can also cause pneumonia, whereas filtering the aspirate to remove particulate matter without altering its neutral pH can reduce the pulmonary injury to minimal levels (3, 4). Similarly, aspiration of particulate antacids has also been shown to cause pneumonitis (5).

In view of the advantages of preoperative neutralization of stomach contents and the dangers of particulate aspiration, we compared the potential for lung damage following aspiration of particulate and soluble antacids. We compared, in rabbits, the changes in arterial blood gas tensions and lung pathology following tracheal instillation of antacids, hydrochloric acid, or saline.

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Received from the Departments of Anesthesiology and Pathology, University of California, Irvine, Medical Center, Orange, California. Accepted for publication November 10, 1981.
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Methods and Materials

Twenty-four male New Zealand White rabbits, ranging in weight from 2.0 kg to 2.6 kg, were studied. The rabbits were randomly assigned to one of four groups (five rabbits each) each of which received a different aspirate, or to a control group (four rabbits) which underwent a sham aspiration. Rabbits in group I received 4 ml of sterile normal saline, pH 6.5. Rabbits in group II received 2 ml of hydrochloric acid, pH 1.5, mixed with 2 ml of Mylanta. Mylanta is a particulate suspension containing 40 mg/ml of magnesium hydroxide, 40 mg/ml of aluminum hydroxide, and 4 mg/ml of simethicone. The pH of this acid-antacid mixture was 7.2. Rabbits in group III received 4 ml of hydrochloric acid, pH 1.5, and rabbits in group IV received 2 ml of hydrochloric acid, pH 1.5, mixed with 2 ml of half-strength Bicitra. Bicitra is a clear liquid containing 1 M sodium citrate and 0.6 M citric acid in a sugar-free base. The pH of this acid-antacid mixture was 4.2. Rabbits in group V received no aspirate.

All rabbits were examined to ensure that they were in good health and that there were no signs of respiratory infection. Institutional standards for the care of laboratory animals were followed. After an overnight fast, each rabbit was weighed and arterial blood was drawn from the central artery of the ear. The rabbit was then sedated with ketamine, 100 mg, intramuscularly and restrained, and the trachea was intubated

under direct vision. A small feeding tube was inserted until its tip protruded just beyond the end of the tracheal tube. With the animal in the supine position, the test mixture (4 ml) was instilled slowly into the lungs, followed by 4 ml of air. Four control rabbits were subjected to the same procedure except that nothing was instilled into the trachea. Following tracheal instillation the feeding and tracheal tubes were removed and the animals were allowed to recover. Arterial blood samples were drawn 15 minutes, and 4 and 48 hours following aspiration. The animals received no other therapy. Forty-eight hours after aspiration, each rabbit was killed by an intramuscular injection of ketamine, 100 mg, and succinylcholine, 20 mg. The lungs and trachea were immediately removed, weighed, and examined for gross pathology. Each lung lobe was individually scored as follows: 0, no gross pathology; 1, congestion without consolidation; 2, focal sparse consolidation; 3, diffuse prominent consolidation. The lungs were then fixed by instillation of 10% formalin into the trachea with a hydrostatic pressure of 10 cm. Representative sections were stained with hematoxylin and eosin and examined by light microscopy. Each lobe was scored from 0 to 4 based on the extent of intra-alveolar pneumonia, interstitial edema and infarction, bronchiolar necrosis, and bronchitis with peribronchitis. Both gross and microscopic examinations of lung tissue were performed by a pathologist who was not aware of the mixture aspirated.

Finally, samples of both antacids were cultured in thioglycolate broth (with vitamin K_1 and hemin added) and on blood agar plates. Statistical analysis was performed using Student's *t*-test for unpaired data.

Results

Twenty-two rabbits survived until killed 48 hours after aspiration. One rabbit died approximately 8 hours after aspiration of particulate antacid. This animal's Pa_{O_2} 4 hours after aspiration was 30.8 mm Hg (the lowest value recorded in any rabbit) and the animal was in obvious respiratory distress. One rabbit, from the control group, was killed early due to inadvertant spinal cord injury.

Pathology

Pathology data are shown in Table 1. Mean body weights of rabbits in each group were not statistically different. Mean lung weights, however, were significantly greater in all groups subjected to aspiration than in control animals. The mean lung weight of rabbits in group II (particulate antacid) was significantly higher than those of all other groups.

The gross pathology score indicates the average number of lung lobes (of the five lobes per rabbit) that showed consolidation (focal or diffuse). Scores for rabbits in groups II (particulate antacid) and III (HCl) were significantly higher than for group V (control), whereas scores for rabbits in groups I (saline) and IV (soluble antacid) were not.

The microscopic pathology score similarly indicates the average number of lung lobes that showed severe pathologic changes (scores of 3 or 4). The score for rabbits in group II (particulate antacid) was significantly higher than all other groups.

The substance aspirated did not influence the character of the intra-alveolar pneumonia, which consisted of an exudate predominated by numerous young and old macrophages with degenerating polymorphonuclear leukocytes and scattered eosinophils. Interstitial infiltration by the same cell population plus edema was a prominent feature of the most severely affected lobes. Representative sections from group II (particulate antacid) and group IV (soluble antacid) are shown in Figs 1 and 2, respectively. Fig 1 shows severe

TABLE 1
Pulmonary Pathology 48 Hours after Aspiration*

Group	Aspirate	Animal weight	Lung weight	Gross pathology score†	Microscopic pathology score†
		kg	*g*		
I	Saline	2.38 ± 0.20	16.0 ± 2.1‡	1.6 ± 1.5	0.2 ± 0.4
II	Mylanta	2.29 ± 0.14	23.9 ± 2.9§	4.8 ± 0.5‡	4.0 ± 0.8§
III	HCl	2.32 ± 0.12	16.1 ± 0.5‡	2.8 ± 1.5‡	0.6 ± 0.9
IV	Bicitra	2.30 ± 0.21	14.7 ± 2.2‡	2.6 ± 1.9	0.8 ± 0.8
V	Sham	2.36 ± 0.20	10.5 ± 0.3	0 ± 0	0 ± 0

* Values are means ± SD.
† See text for definitions.
‡ $p < 0.05$ compared with sham aspiration group.
§ $p < 0.01$ compared with all other groups.

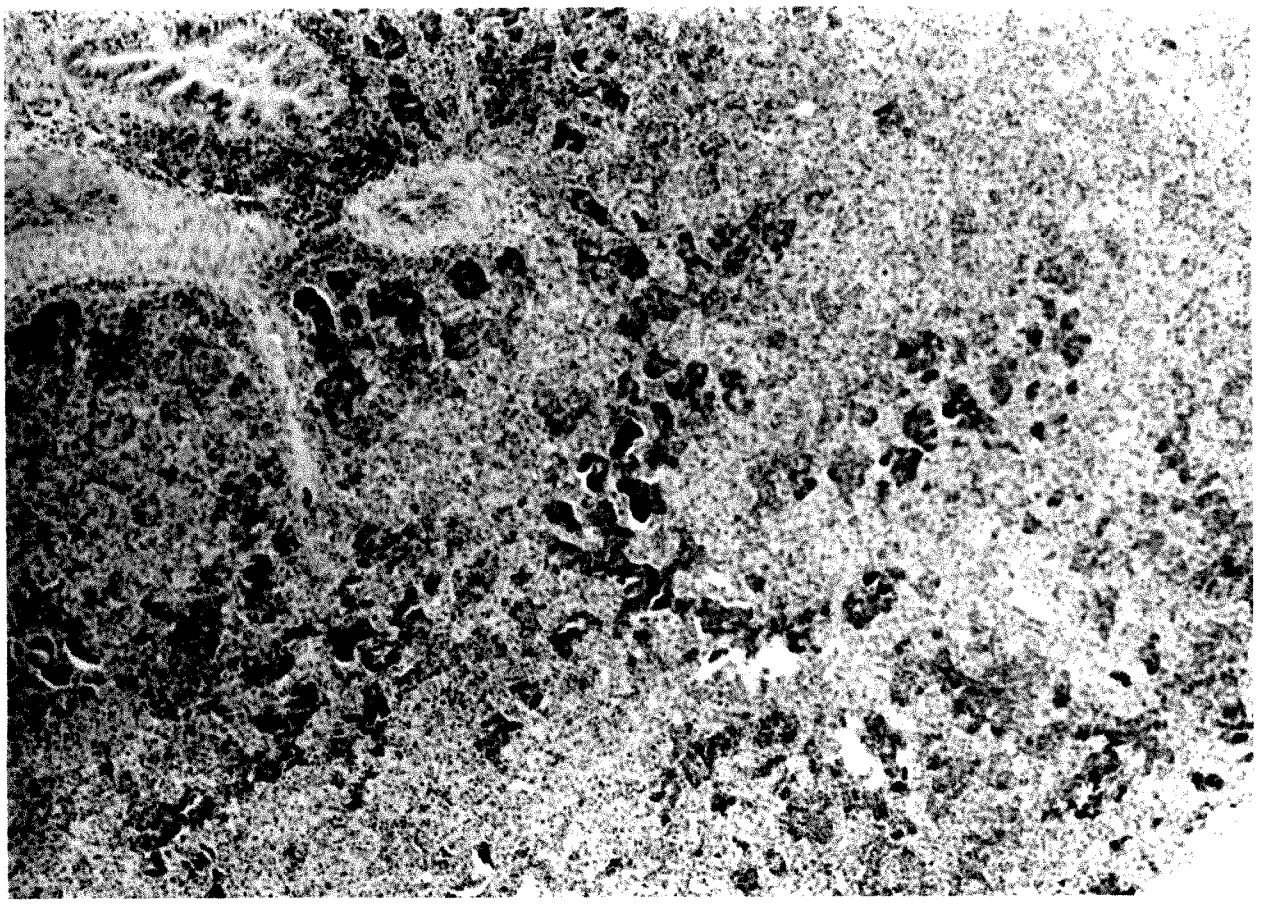


FIG 1. Diffuse infiltration of lung parenchyma by macrophages and polymorphonuclear leukocytes and destruction of alveolar architecture 48 hours after Mylanta aspiration. 250×.

intra-alveolar pneumonia with destruction of alveolar architecture and bronchiolar necrosis. It had a score of 4. Fig 2 shows mild patchy intra-alveolar pneumonia, preservation of alveolar architecture, mild-to-moderate interstitial edema, no bronchiolar necrosis, but absent or mild bronchitis. It had a score of 2.

Arterial Blood Gas Tensions

Arterial oxygen tensions are shown in Table 2. The average Pa_{O_2} of rabbits in group V (control) was greater than 84 mm Hg at each sample time and did not change significantly. Animals in all other groups showed average control Pa_{O_2} values of 74 to 90 mm Hg which decreased to 53 to 59 mm Hg 15 minutes after aspiration. The Pa_{O_2} in each group that received an aspirate was significantly less than that in control animals at the same time.

Four hours after aspiration, Pa_{O_2} in rabbits in group I (saline) had returned to control levels. In the other three aspiration groups mean Pa_{O_2} levels remained significantly lower than in control animals and, in addition, mean Pa_{O_2} in rabbits in group II (particulate antacid) was significantly lower than in group IV (soluble antacid).

Forty-eight hours after aspiration, Pa_{O_2} was significantly lower than in control animals only in rabbits in group II (particulate antacid).

Fifteen minutes after aspiration, arterial pH decreased slightly in rabbits in group I (saline), group II (particulate antacid), and group V (control), and Pa_{CO_2} increased slightly in group II (particulate antacid). Four hours after aspiration pH and Pa_{CO_2} values had returned to control levels in all groups.

Bacterial Culture

The antacid cultures were observed for 3 days each and revealed no growth.

Discussion

Pulmonary aspiration of stomach contents can cause hypoxemia, bronchospasm, pulmonary infil-

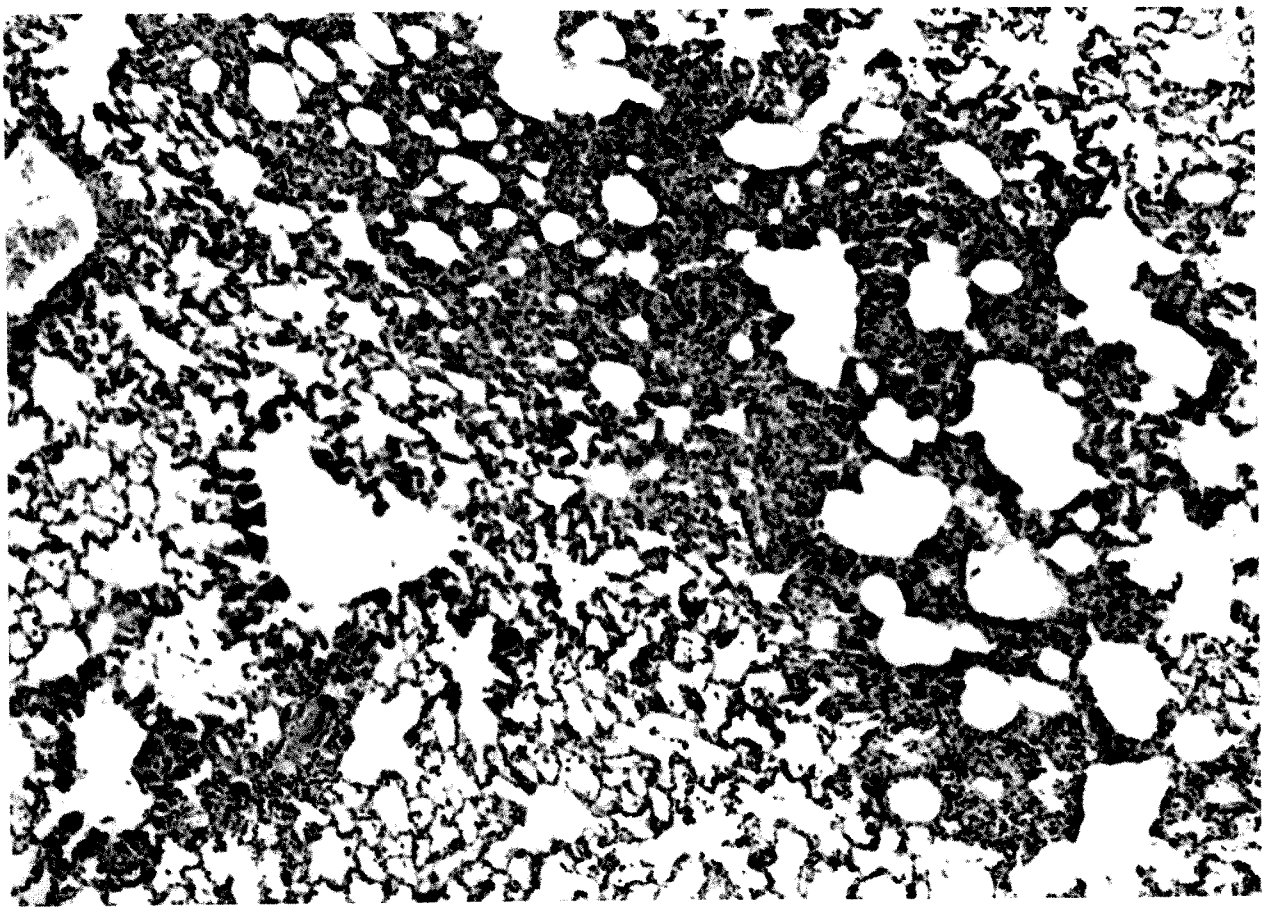


FIG 2. Patchy intra-alveolar pneumonia, interstitial inflammation, and edema 48 hours after Bicitra aspiration.

TABLE 2
Arterial Oxygen Tensions before and at Intervals after Aspiration*

Group	Aspirate	Pa_{O_2}			
		Awake control	15 min	4 hr	48 hr
		mm Hg			
I	Saline	74 ± 5	57 ± 21†	89 ± 29	86 ± 30
II	Mylanta	90 ± 20	53 ± 15†	44 ± 14†‡	56 ± 8†
III	HCl	80 ± 4	59 ± 15†	58 ± 9†	66 ± 15
IV	Bicitra	83 ± 15	58 ± 6†	67 ± 6†	85 ± 36
V	Sham	115 ± 21	85 ± 10	85 ± 3	84 ± 8

* Values are means ± SD.
† $p < 0.05$ compared with sham aspiration group.
‡ $p < 0.05$ Mylanta vs saline, and $p < 0.05$ Mylanta vs Bicitra.

trates, and even death, despite the prior administration of antacids (6–8). Such cases may represent the sequelae of aspiration of neutral food particles, a situation difficult at times to distinguish clinically from acid aspiration (4). Other possibilities are that the stomach pH may have been inadequately neutralized, or that the antacid may itself have contributed to the pulmonary injury.

Several investigators have demonstrated pulmonary pathology following aspiration of particulate antacids. Taylor and Pryse-Davies (9) demonstrated severe pulmonary consolidation in rats after aspirating antacids containing magnesium trisilicate or aluminum hydroxide. Wheatley et al (10) studied the effects in rats of aspiration of gastric contents (pH 1.4) or gastric contents neutralized to pH 8.7 with milk of magnesia (magnesium hydroxide) and found similar histologic changes of acute inflammation in both groups. Gibbs et al (5) compared the effects in dogs of acid aspiration and aspiration of a magnesium hydroxide-aluminum hydroxide antacid and found that the acid produced a hemorrhagic inflammation, whereas the antacid produced a severe bronchopneumonia. When examined 1 month after aspiration, the acid-induced pathology had resolved, whereas lungs from animals given antacid showed persistent infiltrates. In Gibbs' study, the antacid produced decreases in arterial oxygenation which were similar in severity to the decreases resulting from acid aspiration.

The pulmonary effects of aspiration of soluble antacids have been less well investigated. Lahiri et al (11)

found little lung pathology in rats after tracheal instillation of 0.3 M sodium citrate, but the model also failed to detect significant pathology when 0.1 N HCl was used as the aspirate.

The above studies indicate that aspiration of a variety of particulate antacids can cause pulmonary injury, and Cohen (12) has emphasized the potential clinical hazards of administration of particulate antacids to parturients. However, the lesser potential of soluble antacids to produce lung damage when aspirated has not previously been demonstrated.

The present study compared the effects of aspiration of a particulate magnesium hydroxide-aluminum hydroxide antacid and a soluble citrate antacid and found significantly greater lung weights, more severe gross and microscopic pathologic changes, and lower arterial oxygen tensions following the particulate antacid aspiration. Citrate antacids are therefore preferred over magnesium hydroxide-aluminum hydroxide antacids for preoperative use in situations in which the citrate antacid can be shown to be effective in neutralizing stomach contents.

Decreases in arterial oxygen tension following the aspiration of the magnesium hydroxide-aluminum hydroxide antacid were shown, as in Gibbs' study (5), to be similar to those following aspiration of hydrochloric acid (pH 1.5). In addition, the present study demonstrated more severe lung pathology following aspiration of the particulate antacid than following acid aspiration. Omitting antacids may therefore be preferable to the preoperative use of magnesium hydroxide-aluminum hydroxide antacids.

ACKNOWLEDGMENTS

Samples of Bicitra were provided by the Willen Drug Company, Baltimore, MD.

The authors wish to acknowledge the invaluable technical help of June Zaccari, BS.

REFERENCES

1. Mendelson CL. The aspiration of stomach contents into the lungs during obstetric anesthesia. Am J Obstet Gynecol 1946;52:191–205.
2. Roberts RB, Shirley MA. Reducing the risk of acid aspiration during cesarean section. Anesth Analg 1974;53:859–68.
3. Teabeaut JR II. Aspiration of gastric contents. Am J Pathol 1952;28:51–67.
4. Wynne JW, Modell JH. Respiratory aspiration of stomach contents. Ann Intern Med 1977;87:466–74.
5. Gibbs CP, Schwartz DJ, Wynne JW, Hood CI, Kuck EJ. Antacid pulmonary aspiration in the dog. Anesthesiology 1979;51:380–5.
6. Bond VK, Stoelting RK, Gupta CD. Pulmonary aspiration syndrome after inhalation of gastric fluid containing antacids. Anesthesiology 1979;51:452–3.
7. Taylor G. Acid pulmonary aspiration syndrome after antacids. Br J Anaesth 1975;47:615–7.
8. Whittington RM, Robinson JS, Thompson JM. Fatal aspiration (Mendelson's) syndrome despite antacids and cricoid pressure. Lancet 1979;2:228–30.
9. Taylor G, Pryse-Davies J. The prophylactic use of antacids in the prevention of the acid-pulmonary-aspiration syndrome (Mendelson's syndrome). Lancet 1966;1:288–91.
10. Wheatley RG, Kallus FT, Reynolds RC, Geisecke AH. Milk of magnesia is an effective preinduction antacid in obstetric anesthesia. Anesthesiology 1979;50:514–9.
11. Lahiri SK, Thomas TA, Hodgson RMH. Single-dose antacid therapy for the prevention of Mendelson's syndrome. Br J Anaesth 1973;45:1143–6.
12. Cohen SE. Aspiration syndromes in pregnancy. Anesthesiology 1979;51:375–7.

technical
COMMUNICATION

Jet Pulse Characteristics for High-Frequency Jet Ventilation in Dogs

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High-frequency jet ventilation (HFJV) delivers pulsed gas streams to the airway either via small diameter catheters placed inside or via a lumen contained within the wall of a tracheal tube (1–3). Pulsation of the HFJV source gas is typically produced by either electronic-controlled solenoid valves or fluidic systems that can provide precise regulation of the pulsed gas stream (1–7). Frequencies may be independently prescribed or electronically coupled to the cardiac QRS complex (5, 6).

HFJV reportedly provides efficient ventilation at peak airway pressures and tidal volumes significantly less than those required for conventional ventilation (8). Effectiveness of HFJV has been correlated with high flow amplitude, high initial inspiratory flow, and sufficient expiratory time (I/E) $\geq$ 0.3) (7).

The purpose of this study was to investigate high-frequency jet characteristics upon ventilation efficiency using constant gas inlet pressures in dogs. Effects of the solenoid-controlled independent variables (pulse duration, frequency, and wave shape) were observed upon dependent variables [airway peak pressure, positive end-expiratory pressure (PEEP), change of airway pressure (Peak − PEEP = Δ airway pressure), expiratory flow rates, and arterial blood gas tensions (Pa_{O_2}, Pa_{CO_2})]. The variables were chosen because of potential clinical usefulness for high-frequency ventilator settings.

Methods

Six mongrel dogs (6.8 to 20.4 kg each) were anesthetized (thiopental, 5 mg/kg, with subsequent additional doses of 1 mg/kg as required plus chlorpromazine, 0.5 mg/kg), paralyzed (pancuronium, 0.1 mg/kg, repeated as appropriate), and studied after tracheal intubation (9-mm tracheal tubes) and cannulation of a femoral vein (for drugs and crystalloid at a rate of 5 ml/kg/hr) and a femoral artery (for measurements of blood gas tensions and blood pressure).

The electromechanical HFJV system used for this study is shown in Fig 1. A 3-mm i.d. polyethylene catheter passed 10 cm beyond the vocal cords before and outside the tracheal tube and connected to a tranducer and recording system with frequency response of greater than 100 Hz which was used to measure peak and positive end-expiratory airway pressures (PEEP). The pulsed gas streams were delivered by a similar catheter which was passed through the wall of the tracheal tube to its distal tip and proximally connected to an open anesthesia circuit. The proximal end of the ventilating catheter was connected to a programmable solenoid driven by an oxygen source regulated to approximately 1.25 psi/kg of dog weight. At each of three frequencies (120, 150, 180 min^{-1}) three inspiratory pulse durations (0.05, 0.10, 0.13 seconds) were studied. These values corresponded to nine inspiratory/expiratory time (I/E) ratios: 0.11, 0.14, 0.18, 0.25, 0.33, 0.35, 0.43, 0.48, 0.65 where I/E = pulse duration/(1.0/frequency − pulse duration).

A noncompliant 125-ml capacitor (bottle) placed in the circuit distal to the solenoid and proximal to the jet catheter resulted in a damped sinusoidal/sawtooth wave shape. Thus 18 settings (two wave shapes, three durations, three frequencies) were studied in random

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Received from the Department of Anesthesiology, University of Arizona Health Sciences Center, Tucson, Arizona 85724. Accepted for publication November 16, 1981.
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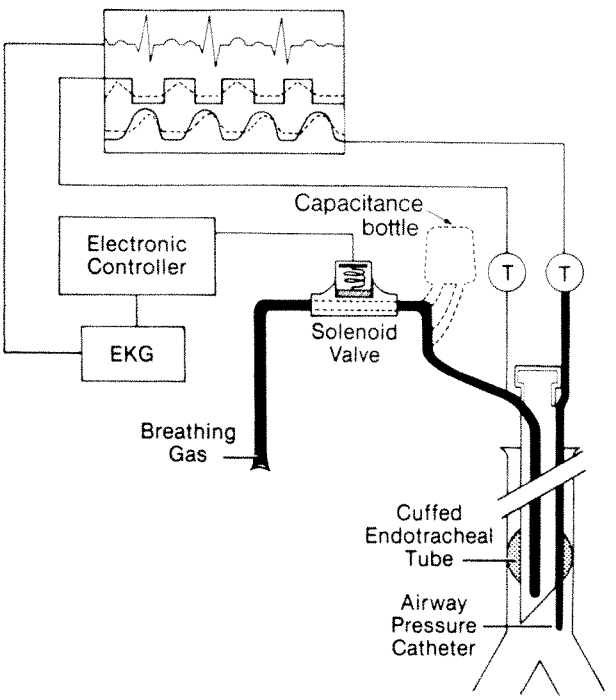


FIG 1. Schematic diagram of experimental HFJV system. Jet was introduced at distal tip of tracheal tube and pulsed by electronically controlled solenoid valve. Airway pressures were measured via transducer (T) attached to a small catheter outside endotracheal (ET) tube. Circuit pressures were measured via transducer (T) attached between solenoid valve and jet. ECG and pressures were displayed on oscilloscope. To produce a sawtooth wave shape, a 125-ml bottle capacitor (dotted lines) was inserted distal to solenoid in jet supply line. Dotted curves are indicative of shapes produced by bottle.

sequence in each dog. After 15 minutes at each setting, arterial blood gas tensions and expiratory gas flow rates (Bourns LS-75) were determined. Intra-airway pressure, arterial blood pressure, chest expansion (impedance plethysmography), and electrocardiogram were continuously recorded. Intra-airway pressures were determined as peak, end-expiratory (PEEP), and the difference between these (Δ airway pressure).

Data were initially analyzed by three-way analysis of variance to determine interactions between independent variables (frequency, pulse duration, wave shape) that would produce observed differences among dependent variables (airway pressures, flow rate, blood gases). Data for each wave shape were analyzed with one-way analysis of variance and a posterior technique (Newman Keuls) for intragroup significance. For given frequency and pulse duration, the data between wave shapes were then compared by paired t-tests. Statistical significance was defined as $p < 0.05$.

Results

Oscilloscopic pressure representations for sawtooth and rectangular wave forms from within a HFJV circuit are shown in Fig 2. Sawtooth wave forms resulted from placement of a 125-ml bottle as a capacitor distal to the solenoid but proximal to the jet catheter. Pressure, flow, and blood gas data are shown in Table 1 for rectangular wave HFJV and in Table 2 for sawtooth wave HFJV. These data are shown graphically in Figs 3 to 8.

Airway pressures at differing frequencies and wave shapes are shown as functions of pulse duration (Fig 3) and I/E (Fig 4). Statistically significant differences in peak, end-expiratory, and Δ airway pressures among I/E groups are described in Table 3 (rectangular wave) and Table 4 (sawtooth wave) with statistical differences between wave shape groups given in Table 5. Generally, higher pressures occurred as pulse duration, frequency, and I/E increased. For a rectangular wave shape, statistically higher peak airway pressures (>7.4 cm H_2O) occurred at I/E > 0.35 with the highest PEEP (3 cm H_2O) at an I/E of 0.65. The greatest Δ airway pressure (5 cm H_2O) occurred at 0.13 seconds duration and 120 min^{-1} (I/E = 0.35). With the sawtooth wave shape, the highest peak airway pressures (>6 cm H_2O) were obtained at I/E > 0.33 with the largest values for both PEEP (3.6 cm H_2O) and Δ airway pressures (4.3 cm H_2O) occurring at a 0.13 seconds duration at 180 min^{-1} (I/E = 0.65). Significant differences between wave shapes (Table 5) reveal higher peak, lower end-expiratory, and greater Δ airway pressures occurring with rectangular compared with sawtooth wave shapes.

In Figs 5 and 6, expiratory flow rate results are presented with statistical data in Tables 3 to 5. Measured expiratory flow includes both jet and entrained gas and does not necessarily indicate flow within airways. Flow generally increased with increasing duration, frequency, and I/E. At the lower I/E (<0.25), flows resulting from rectangular waves are greater

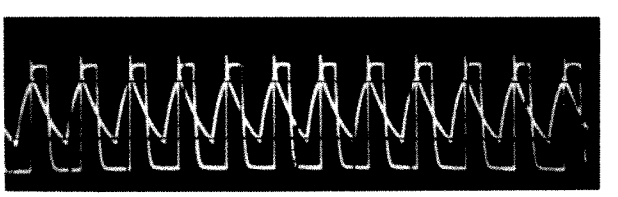


FIG 2. Rectangular wave and sawtooth wave pressure pulses. Superimposed gas pressure pulses were recorded in the circuit in absence (rectangular wave) and presence (sawtooth wave) of 125-ml bottle. Both rectangular and sawtooth waves caused peak airway pressures of 6 to 7 cm H_2O.

TABLE 1

Effects of Rectangular Wave Pulse Duration and Frequency on Airway Pressures, Flows, and Arterial Blood Gas Tensions*

Group	Pulse	Frequency	I/E†	Flow	Peak	Δ Pressure	PEEP	Pa_{O_2}	Pa_{CO_2}
	sec	*min*$^{-1}$		*L/min*		*cm* H_2O			*torr*
1	0.05	120	0.11	7.8 ± 1.1	5.0 ± 0.5	3.6 ± 0.6	1.4 ± 0.3	429 ± 51	63.7 ± 14.6
2	0.05	150	0.14	10.6 ± 1.7	5.3 ± 0.5	3.8 ± 0.7	1.6 ± 0.3	420 ± 45	56.6 ± 12.0
3	0.05	180	0.18	13.5 ± 2.4	5.5 ± 0.6	3.7 ± 0.7	1.9 ± 0.3	468 ± 49	50.3 ± 8.1
4	0.10	120	0.25	12.5 ± 1.8	6.0 ± 0.4	4.3 ± 0.6	1.7 ± 0.3	446 ± 43	47.3 ± 8.2
5	0.10	150	0.33	15.7 ± 2.1	6.9 ± 0.3	4.8 ± 0.2	2.1 ± 0.4	423 ± 39	46.8 ± 8.1
6	0.10	180	0.43	17.2 ± 2.5	7.2 ± 0.3	4.7 ± 0.5	2.5 ± 0.5	457 ± 48	43.2 ± 5.7
7	0.13	120	0.35	11.6 ± 1.3	7.4 ± 0.5	5.0 ± 0.8	2.4 ± 0.4	472 ± 51	30.1 ± 3.1
8	0.13	150	0.48	12.6 ± 0.6	6.9 ± 0.5	4.3 ± 0.7	2.6 ± 0.3	439 ± 42	33.1 ± 3.7
9	0.13	180	0.65	15.0 ± 0.5	7.7 ± 0.6	4.8 ± 0.6	3.0 ± 0.3	481 ± 45	36.1 ± 5.4

* Values are means ± SEM.

† I/E = pulse duration / (1.0/frequency − pulse duration).

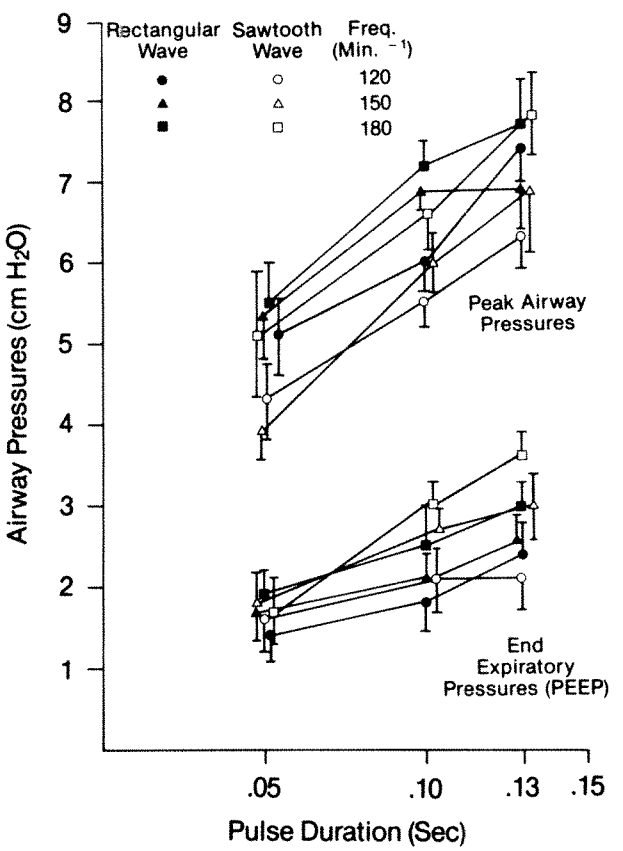


FIG 3. Airway pressures (mean ± SEM) as functions of frequency, wave shape, and pulse duration. For a given wave shape, increases in pulse duration and frequency tend to increase airway pressures. Statistical significance is discussed in text and Tables 3 to 5. Only single SEM flags are shown for clarity in Figs 3 to 8.

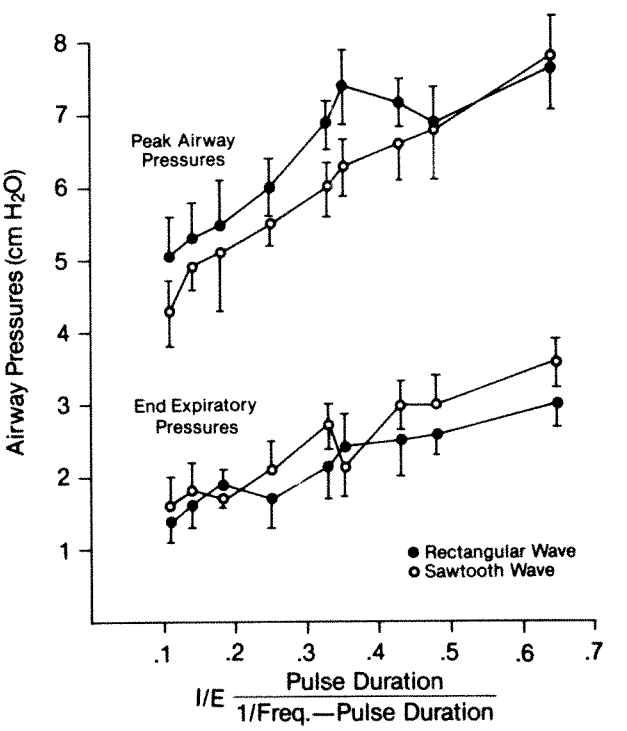


FIG 4. Effects of I/E on airway pressures (mean ± SEM). Increasing I/E correlates with increases in airway pressures. Statistical significance is discussed in text and Tables 3 to 5.

than those associated with sawtooth waves (12.5 vs 10.0 L/min). At I/E > 0.25, the flows produced by the two wave shapes were not significantly different.

Pa_{CO_2} data are shown in Figs 7 and 8 with statistical analyses in Tables 3 to 5. In general, Pa_{CO_2} values tended to be lower as duration, frequency, and I/E increased. Rectangular wave HFJV yielded lower Pa_{CO_2} levels than did sawtooth wave HJFV at several I/E values (0.25, 0.35, 0.43, 0.48). Few intragroup differences were statistically significant, although the highest mean Pa_{CO_2} values (63.7 torr) occurred at the smallest I/E of 0.11 (0.05 seconds, 120 min^{-1}) for the rectangular wave and at a slightly larger I/E of 0.18 (0.05 seconds, 180 min^{-1}) for sawtooth wave HFJV (97.3 torr).

Pa_{O_2} varied only slightly with differing I/E ratios

TABLE 2

Effects of Sawtooth Wave Pulse Duration and Frequency on Airway Pressures, Flows, and Arterial Blood Gas Tensions*

Group	Pulse	Frequency	I/E†	Flow	Peak	Δ Pressure	PEEP	Pa_{O_2}	Pa_{CO_2}
	sec	*min*$^{-1}$		*L/min*		*cm* H_2O			*torr*
1	0.05	120	0.11	7.1 ± 1.5	4.3 ± 0.5	2.6 ± 0.4	1.6 ± 0.4	460 ± 69	73.8 ± 22.0
2	0.05	150	0.14	7.3 ± 1.6	3.9 ± 0.3	2.1 ± 0.4	1.8 ± 0.4	413 ± 55	66.8 ± 16.4
3	0.05	180	0.18	8.9 ± 1.7	5.1 ± 0.8	3.4 ± 0.7	1.7 ± 0.4	451 ± 63	97.3 ± 33.4
4	0.10	120	0.25	10.0 ± 1.1	5.5 ± 0.3	3.5 ± 0.5	2.1 ± 0.4	439 ± 54	79.1 ± 19.0
5	0.10	150	0.33	13.0 ± 1.4	6.0 ± 0.4	3.4 ± 0.4	2.7 ± 0.3	441 ± 57	71.4 ± 17.3
6	0.10	180	0.43	14.4 ± 1.4	6.6 ± 0.5	3.7 ± 0.5	3.0 ± 0.3	443 ± 41	84.0 ± 19.3
7	0.13	120	0.35	11.2 ± 1.2	6.3 ± 0.4	4.2 ± 0.3	2.1 ± 0.4	450 ± 34	55.9 ± 8.9
8	0.13	150	0.48	15.1 ± 1.8	6.9 ± 0.8	3.8 ± 0.7	3.0 ± 0.4	458 ± 41	67.8 ± 11.3
9	0.13	180	0.65	16.9 ± 1.5	7.8 ± 0.5	4.3 ± 0.6	3.6 ± 0.3	437 ± 48	77.8 ± 19.4

* Values are means ± SEM.

† I/E = pulse duration / (1.0/Frequency − pulse duration).

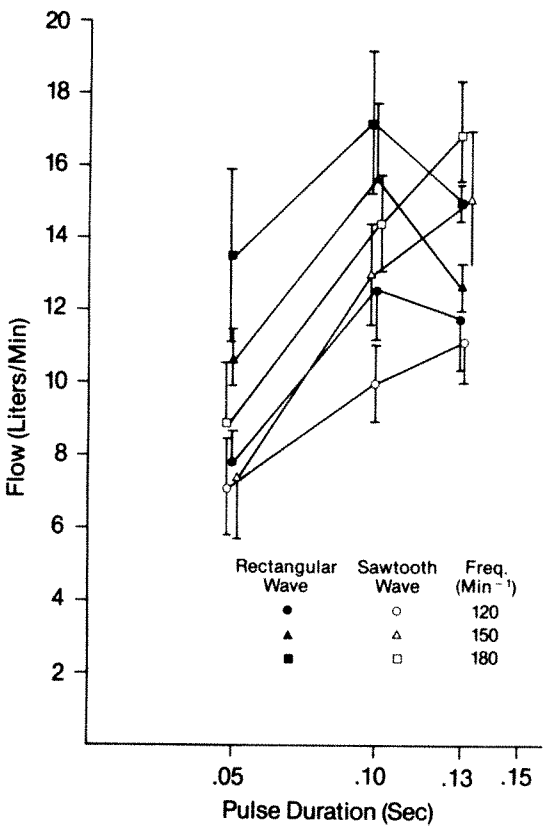


FIG 5. Expiratory flow rate (mean ± SEM) as function of pulse duration, frequency, and wave shape. Increasing pulse duration and frequency correlate with increases in expiratory flow rate. Expiratory flow rate includes entrained gas and does not necessarily indicate distal airway flow. Statistical significance is discussed in text and Tables 3 to 5.

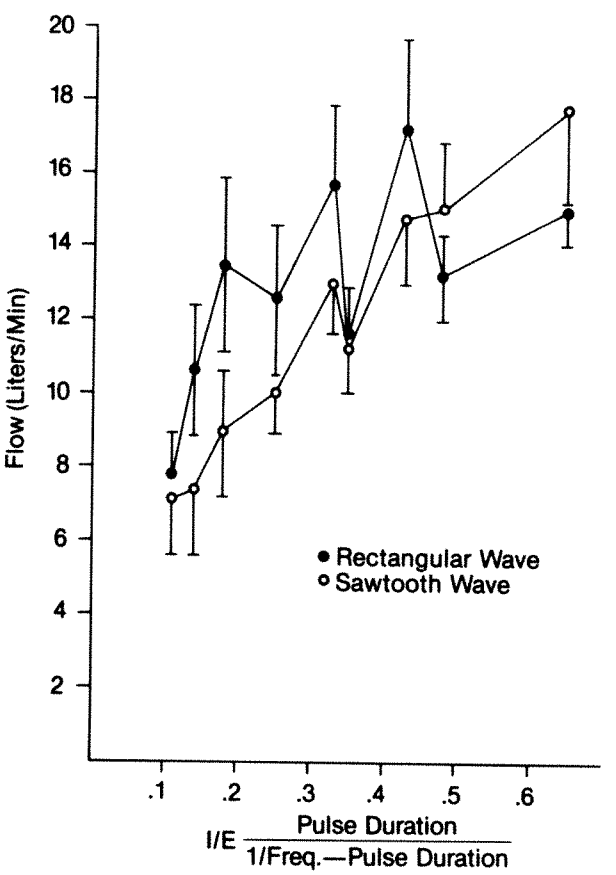


FIG 6. Effect of I/E on expiratory flow rates (mean ± SEM). Increasing I/E correlates with increased expiratory flow rate. Statistical significance is discussed in text and Tables 3 to 5.

and wave shapes (Tables 1 to 5). For rectangular wave HFJV, highest Pa_{O_2} (481 torr) levels occurred at an I/E of 0.65 (0.13 seconds, 180 min^{-1}) whereas sawtooth wave HFJV had the highest Pa_{O_2} (460 torr) at an I/E of 0.11 (0.05 seconds, 120 min^{-1}). The only significant wave shape difference occurred at an I/E of 0.65 at which rectangular HFJV Pa_{O_2} was higher than the Pa_{O_2} produced by the sawtooth (481 vs 437 torr).

Analysis of variance showed no three-way interactions and a single two-way interaction (wave shape and pulse duration on flow, $p = 0.04$). Independent effects ($p < 0.01$) included: frequency and duration

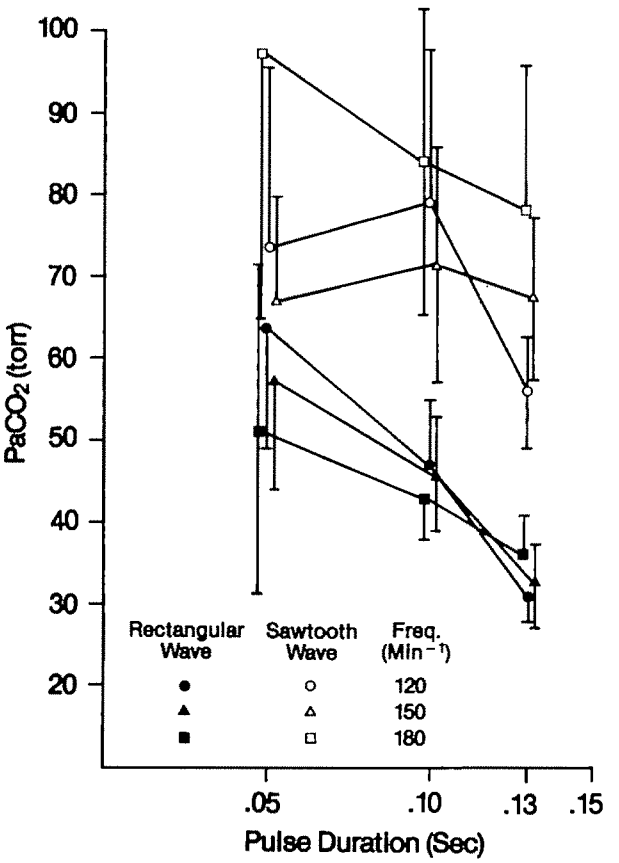


FIG 7. Pa_{CO_2} (mean ± SEM) as function of pulse duration, frequency, and wave shape. Rectangular wave shapes resulted in lower Pa_{CO_2} levels than did sawtooth wave shapes. Statistical significance is discussed in text and Tables 3 to 5.

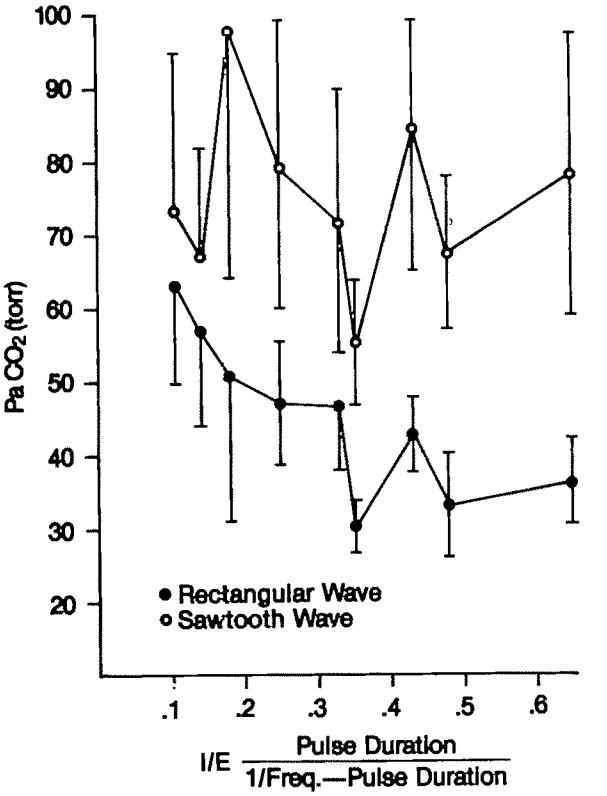


FIG 8. Effect of I/E on Pa_{CO_2} (mean ± SEM). Pa_{CO_2} value resulting from rectangular waves were generally lower than they were with sawtooth waves at a given I/E. Statistical significance is discussed in text and Tables 3 to 5.

on flow; frequency, duration, and wave shape on peak airway pressure and PEEP; and duration and wave shape on Δ airway pressure and Pa_{CO_2}.

At some pulse duration and frequency conditions, HFJV-related phasic variations in heart rate, arterial blood pressure, and chest expansion were observed. Typical wave shape patterns are shown in Fig 9 with conditions for a single dog presented in Table 6. With the rectangular wave, HFJV fluctuations in amplitude of chest expansion generally occurred. Analysis of oscillographic tracings of these phasic fluctuations showed a typical "beat frequency envelope" (mathematically the difference of two sine waves). Maximal chest expansion occurred when peak airway pressure coincided with diastole. Maxima and minima in chest expansion occurred periodically as beat frequencies at a rate equal to the difference between heart rate and HFJV rate (Fig 9). Amplitude of the chest expansion also varied with PEEP, with greatest movement occurring with PEEP < 3 cm H_2O or Δ airway pressure > 3 cm H_2O. Phasic changes in arterial blood pressure commonly occurred with sawtooth wave HFJV at a PEEP > 3 cm H_2O. These phasic fluctuations of blood pressures were periodic, but not at a predictable or identifiable beat frequency.

TABLE 3

Comparison of Results between Groups for Rectangular Waves*

1. Flow rate (L/min)				
Group 1	7.8 ± 1.1	<	group 5	15.7 ± 2.1
			group 6	17.2 ± 2.5
2. Peak airway pressure (cm H_2O)				
A. Group 1	5.1 ± 0.5		group 6	7.2 ± 0.3
Group 2	5.3 ± 0.5	<	group 7	7.4 ± 0.5
Group 3	5.5 ± 0.6		group 9	7.7 ± 0.6
B. Group 1		<	groups 6, 7	
C. Groups 2, 3		<	group 9	
3. PEEP (cm H_2O)				
Group 9	3.0 ± 0.3	>	any group 1–8	
4. Airway pressure (cm H_2O)				
Group 7	5.0 ± 0.8	>	group 1–6, 8, 9	
5. Pa_{O_2} (torr)				
Group 9	481 ± 45	>	any group 1–8	
6. Pa_{CO_2} (torr)				
Group 1	63.7 ± 14.6	>	any group 2–9	

* Groups are defined in Tables 1 and 2; $p \leq 0.05$.

TABLE 4

Comparison of Results between Groups for Sawtooth Waves*

1. Flow rate (L/min)				
A. Group 1	7.1 ± 1.5			
Group 2	7.3 ± 1.6		group 6	14.4 ± 1.4
Group 3	8.9 ± 1.7	<	group 8	15.1 ± 1.8
Group 4	10.0 ± 1.1		group 9	16.9 ± 1.5
Group 7	11.2 ± 1.2			
B. Groups 1, 2		<	groups 6, 8	
C. Groups 3, 4, 7		<	group 9	
2. Peak airway pressure (cm H_2O)				
A. Group 1	4.3 ± 0.5		group 5	6.0 ± 0.4
Group 2	3.9 ± 0.3		group 6	6.6 ± 0.5
Group 3	5.1 ± 0.8	<	group 7	6.3 ± 0.4
Group 4	5.5 ± 0.3		group 8	6.9 ± 0.8
			group 9	7.8 ± 0.5
B. Groups 1, 3, 4		<	groups 6, 8, 9	
C. Groups 1, 2		<	group 9	
D. Groups 3, 4		<	group 9	
E. Group 2		<	groups 5, 7	
F. Group 1		<	group 8	
3. PEEP (cm H_2O)				
Group 1	1.6 ± 0.4			
Group 2	1.8 ± 0.4	<	group 9	3.6 ± 0.3
Group 3	1.7 ± 0.4			
4. Airway pressure (cm H_2O)				
Group 9	4.3 ± 0.6	>	any group 1–8	
5. Pa_{O_2} (torr)				
Group 1	460 ± 69	>	any group 2–9	
6. Pa_{CO_2} (torr)				
Group 3	97.3 ± 33.4	>	any group 1, 2, 4–9	

* Groups are defined in Tables 1 and 2. $p \leq 0.05$.

TABLE 5

Comparison of Rectangular and Sawtooth Waves*

1. Flow rate (L/min)				
Group 2	10.6 ± 7.1	>	group 2	7.3 ± 1.6
Group 3	13.5 ± 4.1	>	group 3	8.9 ± 1.7
Group 4	12.5 ± 8.1	>	group 4	10.0 ± 1.1
2. Peak airway pressure (cm H_2O)				
Group 2	5.3 ± 0.5	>	group 2	3.9 ± 0.3
3. PEEP (cm H_2O)				
Group 4	1.7 ± 0.3	<	group 4	2.1 ± 0.4
Group 5	2.1 ± 0.4	<	group 5	2.7 ± 0.3
4. Airway pressure (cm H_2O)				
Group 2	3.8 ± 0.7	>	group 2	2.1 ± 0.4
Group 5	4.8 ± 0.2	>	group 5	3.4 ± 0.4
5. Arterial oxygen tension (Pa_{O_2}) (torr)				
Group 9	481 ± 45	>	group 9	437 ± 48
6. Arterial carbon dioxide tension (Pa_{CO_2}) (torr)				
Group 4	47.3 ± 8.2	<	group 4	79.1 ± 19.0
Group 6	43.2 ± 5.7	<	group 6	84.0 ± 19.3
Group 7	30.1 ± 3.1	<	group 7	55.9 ± 8.9
Group 8	33.1 ± 3.7	<	group 8	67.8 ± 11.3

* Groups are defined in Tables 1 and 2, $p \leq 0.05$.

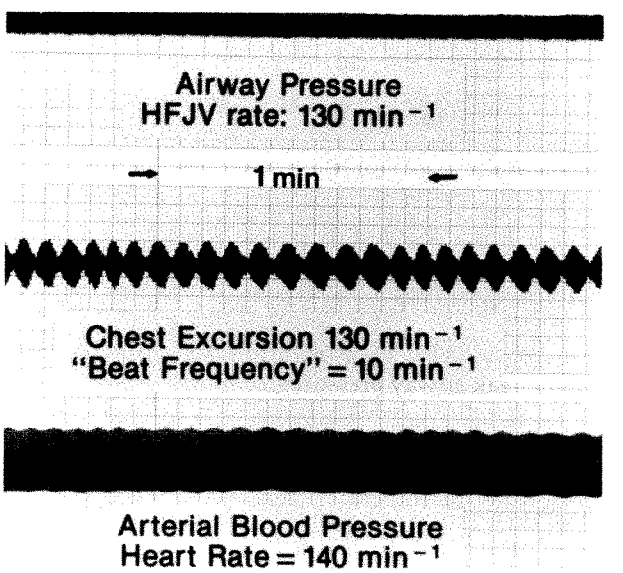


FIG 9. Phasic variations in chest expansion and arterial blood pressure. Chest excursion curve (center) demonstrates a beat frequency envelope (mathematically the difference of two sine waves). Frequency of this wave shape is approximately heart rate minus jet frequency (140 − 130 = 10 min^{-1}). Blood pressure curve (bottom) demonstrates phasic variation (not beat frequency). Associated values for heart rate, airway pressures, and frequencies are given in Table 6.

Discussion

High-frequency ventilation techniques differ from conventional modes and also vary considerably among investigators. Because of variation and lack of standardization of source pressure, flow regulation, jet nozzle size, site of jet introduction into the airway, experimental nimal models, and expiratory resistance, reported results on the effects of jet characteristics such as frequency ranges and inspiratory/expiratory ratios upon flow rates and airway pressures are confusing.

In the present HFJV study, gas source pressure (1.25 psi/kg), jet nozzle size, and jet location in the airway were kept constant. Because of jet location and catheter area compared with tracheal tube area, expiratory resistance was minimal and relatively constant. An electromechanical solenoid valve system was chosen for control purposes. Pulse duration (time solenoid allows jet flow into airway), frequency and wave shape (by capacitance damping) were varied. As HFJV control of tidal volume is difficult, accessible pulse parameters such as duration, pressure amplitude, frequency, and wave shape may become clinically useful high-frequency jet ventilation "settings."

Higher airway pressures and flow rates resulting from increasing pulse duration and frequency (thus

TABLE 6

Phasic Variations in Heart Rate, Systemic Pressure, and Chest Expansion

Pulse duration by wave shape (type)	Frequency	Heart rate	PEAK/PEEP	Phasic type		Difference frequency (HR-HJF)
				CP	BP†	
sec	*min*$^{-1}$		*cm* H_2O			*min*$^{-1}$
Rectangular						
0.05	120	220	6/2	+	−	100
	150	220	4/2	−	−	
	180	180	6/3.5	−	−	
0.1	120	150	6/2.5	+	−	30
	150	125	7.5/4.5	+	+	−25
	180	145	7.5/2	+	−	−35
0.13	120	145	7.5/2.5	+	+	25
	150	140	6/3	+	−	−10
	180	140	5/2	+	−	−40
Sawtooth						
0.05	120	220	5/4	−	−	100
	150	200	4/2.5	−	+	50
	180	210	6/5	−	+	30
0.10	120	140	6/4.5	+	+	20
	150	125	7/6	−	+	−25
	180	150	7/6	−	+	−30
0.13	120	90	7/5	−	+	−30
	150	100	7/6	−	+	−50
	180	120	8/7	−	+	−60

* Appearance of "beat frequency envelope" for chest plethysmograph (CP) recording; + indicates envelope present.

† Appearance of regular phasic pattern in blood pressure (BP) recording; + indicates pattern present.

I/E) are not surprising. At a given complicance, longer pulse durations enable greater gas transport. Similarly, the rapid pulse upstroke and flow time of rectangular waves allow more mass transport (flow) and maintain peak pressures longer, resulting in higher peak airway pressures, Δ airway pressures, and flows than do sawtooth waves. For these pressures, the shorter the expiratory period (jet off), the higher the end-expiration pressure at the initiation of the next cycle. With greater flow and relatively higher expiratory resistance anticipated in adult humans, expiratory time may be more limiting in clinical HFJV and higher I/E values may be ineffective.

At I/E > 0.25, rectangular wave HFJV produced lower Pa_{CO_2} values than did sawtooth wave HFJV. Lowest mean Pa_{CO_2} levels for both rectangular and sawtooth waves occurred with 0.13 seconds and 120 min^{-1} (I/E = 0.35). Maximal peak and Δ airway pressures also occurred at these settings for rectangular waves. Whether these settings are optimal due to cardiac interactions, compliance, or other reasons is unclear. The highest Pa_{CO_2} occurred at the shortest duration (0.05 seconds) for both wave shapes. Pa_{O_2} ranged from 413 to 481 torr and varied slightly among rectangular and sawtooth settings. The only significant difference in Pa_{O_2} between wave shapes (rectangular > sawtooth) occurred at an I/E of 0.65 (PD = 0.13 seconds, F = 180 min^{-1}).

These results imply interactions between peak airway pressures, Δ airway pressures, PEEP, and flow at particular I/E (>0.25) which affect gas exchange. Higher PEEP resulting from higher frequencies, duration, and increased flows may open distal airways to better ventilation but at the risk of increasing dead space and altering lung impedance. Increases in the same variables also produce a significantly greater Δ airway pressure at the large I/E and increase the potential for transmitting HFJV pulse pressure to vascular structures rather than increasing chest expansion. Apparently HFJV must strike a balance between pressure and flow similar to that in conventional ventilation in order to maintain minimum lung volume below which gas exchange becomes inefficient. The relationship of this minimum volume to functional residual and closing capacities is not known

Gas mixing may also be related to mechanical kinetic energy imparted to the airways and lung parenchyma by the jet pulsation. Thus, square wave pulses with high amplitude rapid upstrokes would impart more kinetic energy than sawtooth/PEEP pulses. This may be relevant to the phasic variations in blood pressure and chest excursion (beat frequencies) observed. With rectangular wave pulses and lower PEEP, effective ventilation was associated with phasic HFJV-cardiac interactions in chest expansion. With less efficient sawtooth pulses at higher PEEP, phasic HFJV-cardiac interactions were observed only in arterial blood pressure. PEEP-associated changes in lung volume and compliance may determine impedance and transmission of both HFJV and cardiac mechanical impulses to the airway and lung parenchyma. The lowest Pa_{CO_2} observed occurred for rectangular waves when beat frequencies were also present.

HFJV effectiveness may thus depend on mechanical lung vibration (shaking) and its effect on gas mixing and diffusion. Efficiency of high-frequency, low airway pressure, low tidal volume ventilation has been attributed to enhanced dispersion of respiratory gas molecules (7, 9). Effective dispersion depends on gas concentration gradients, diffusion coefficients, concentrations of other gases, lung pathology, and possibly cardiac oscillations. Several studies (10, 11) indicate that mechanical pulsation of the lungs by cardiac contractions increases effective gas diffusion to

5 times the molecular diffusion coefficient. HFJV with frequencies and tidal volumes similar to heart rate and stroke volumes may similarly enhance dispersion by mechanical shaking of airway walls and lung parenchyma. Enhanced gas mixing and diffusion may be clinically most relevant in medium-sized diseased airways with heterogeneous gas distribution and ventilation-perfusion mismatch (8, 10).

In conclusion, pulse duration, frequency, and wave shape may provide a convenient basis for control of HFJV with airway pressure sensing feedback. In our dog model with negligible expiratory resistance, airway pressures, flow, and ventilation (higher Pa_{O_2}, lower Pa_{CO_2}) generally increased with longer pulse durations, higher frequencies, and greater I/E. HFJV-cardiac interactions may further promote chest movement and gas mixing by kinetic energy effects.

These data from dogs imply that an appropriate I/E ratio (>0.25), peak airway pressures near 10 cm H_2O, and end-expiratory pressures of <3 cm H_2O are required for effective ventilation. General HFJV principles that may be extrapolated to humans suggest the necessity for maintaining a minimum lung volume and compliance for efficient gas exchange, possibly due to recruitment of distal airways, increased flow, and enhanced gas mixing. As expiratory resistance may be more significant in humans, higher I/E values may be clinically ineffective.

ACKNOWLEDGMENTS

The authors would like to acknowledge the contributions of Carolyn Wiseman and Christan Pickering for their assistance in the preparation of this manuscript and the University of Arizona Engineering Research Afiliates Program for technical and financial support.

REFERENCES

1. Sjöstrand U. Review of the physiologic rationale for and development of high frequency positive pressure ventilation—HFJV. Acta Anaesthesiol Scand (Suppl) 1977;64:7–27.
2. Carlson GC, Miodownik S, Ray C, Kahn RC. Technical aspects and clinical implications of high frequency jet ventilation with a solenoid valve. Crit Care Med 1981;9:47–50.
3. Babinski M, Smith RB, Klain M. High frequency jet ventilation for laryngoscopy. Anesthesiology 1980;52:178–80.
4. Klain M, Smith RB. Fluidic technology. Anaesthesia 1976;31:750–7.
5. Klain M, Keszler H. Circulatory assist by high frequency ventilation. Crit Care Med 1980;8:232.
6. Otto CW, Waterson CK, Conahan TJ, Quan SF, Calkins JM, Hameroff SR. Cardiovascular effects of ECG synchronized jet ventilation. Crit Care Med 1981;9:160.
7. Sjöstrand V, Eriksson IA. High rates and low volumes in mechanical ventilation—not just a matter of ventilatory frequency. Anesth Analg 1980;59:567–76.
8. Slutsky AS, Drazen JM, Ingram RH, et al. Effective pulmonary ventilation with small volume oscillations at high frequency. Science 1980;209:609–11.
9. Chang HK. Multicomponent diffusion in the lung. Fed Proc 1980; 39:2759–64.
10. Fukuchi Y, Roussos CS, Macklem PT, et al. Convection, diffusion and cardiogenic mixing of inspired gas in the lung; an experimental approach. Respir Physiol 1976;26:77–90.
11. Engel LA, Menkes H, Wood LDH, et al. Gas mixing during breath-holding studied by intrapulmonary gas sampling. J Appl Physiol 1973;35:9–17.

CLINICAL reports

Anaphylaxis to Meperidine

Jerrold H. Levy, MD,* and Mark A. Rockoff, MD†

Anaphylactic reactions to narcotics are exceedingly rare and have not been previously described with meperidine (1-3). This is a report of such an occurrence and emphasizes the need for prompt recognition and treatment. Confirmation of anaphylaxis was obtained by demonstrating an IgE antibody specific to meperidine.

Case Report

A 2½-year-old, 12-kg girl was scheduled for elective sigmoidoscopy to evaluate rectal bleeding. She was otherwise in excellent health with no allergies or history of asthma. The only known previous exposure to narcotics occurred at 1½ years of age when she was given a cough medication containing codeine. Physical examination was unremarkable.

An intravenous infusion was begun and meperidine, 25 mg, was given intravenously. Within 1 minute, facial urticaria developed associated with coughing. Diphenhydramine, 25 mg, was given, but wheezing and cyanosis rapidly occurred. Oxygen by face mask was begun but cyanosis persisted, pulses became unobtainable, and cardiopulmonary resuscitation was instituted. A tracheal tube was inserted and profuse frothy secretions were suctioned from the trachea. Epinephrine was administered intravenously in repeated doses to a total of 1 mg. Saline, 500 ml, was infused until systolic blood pressure increased to 90 mm Hg. Tonic-clonic seizures developed and were treated with phenobarbital and diazepam. The initial arterial blood gas tensions during ventilation with 100% oxygen were pH 7.25; Pa_{CO_2}, 50 mm Hg; Pa_{O_2}, 80 mm Hg.

The patient was transferred to the pediatric intensive care unit where chest x-ray showed pulmonary edema and an electrocardiogram revealed sinus tachycardia. Mechanical ventilation with 8 cm H_2O positive end-expiratory pressure was instituted. Dexamethasone was administered and an infusion of isoproterenol begun for persistent wheezing. Within 6 hours, mechanical ventilation and the isoproterenol could be discontinued and spontaneous ventilation with an inspired oxygen content of 35% showed arterial pH 7.4; P_{CO_2}, 37 mm Hg; and P_{O_2}, 176 mm Hg. Two generalized seizures were treated with additional diazepam. Twenty-four hours later the patient appeared alert, the chest x-ray revealed resolution of the pulmonary edema, and extubation was accomplished uneventfully. No further seizures occurred and an electroencephalogram was normal. Mild ataxia and weakness resolved over the next 2 days and she was discharged on a regimen of phenobarbital and given a "medi-alert" bracelet. Six weeks later, serum was obtained to detect the presence of IgE antibodies specific for meperidine (RAST or radioallergosorbent test, Iatric Corporation, Tempe, AZ) and was positive (3+/4+). Neurologic examination at this time was normal.

Discussion

This is the first case report of true anaphylaxis developing after meperidine. All signs developed within moments of the intravenous administration of meperidine and no other drugs had been given. A check of this medication confirmed its proper labeling and other patients had received medication from the same vial without adverse effects. The rapid development of urticaria, bronchospasm, cyanosis, and hypotension all supported the clinical diagnosis of anaphylaxis. The presence of IgE antibodies immunospecific for meperidine confirmed the diagnosis.

Although some classes of drugs (e.g., the penicillins) are more frequently responsible for adverse reactions than others, anaphylactic reactions to narcotics

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Received from the Joseph Barr Pediatric Intensive Care Unit and Anesthesia and Children's Services of Massachusetts General Hospital, and Departments of Anesthesia and Pediatrics, Harvard Medical School, Boston, Massachusetts. Accepted for publication October 29, 1981.

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are extremely rare. A review of the medical literature from entries in *Index Medicus* since 1966 fails to contain any documented cases of anaphylaxis following the administration of narcotics. The few reports include simultaneous use of multiple drugs. Codeine is not infrequently one of the drugs, but meperidine has never been implicated. It is unknown why such events occur so rarely with such widely administered agents.

Narcotics, however, may result in a wide variety of untoward effects and mimic anaphylaxis, the so-called anaphylactoid reaction. The term "anaphylaxis" is reserved for those reactions in which evidence exists for an immunospecific antibody (4). Narcotics frequently cause histamine release which produces local effects, such as wheals along the vein of administration, or systemic effects, including orthostatic hypotension. Bronchospasm and respiratory distress do not develop even when large doses of narcotics are used for cardiac anesthesia (5). Heroin abuse may produce pulmonary edema but is probably related to a variety of impurities. Although histamine is one of the substances liberated after an antigen binds immunospecific IgE antibodies on the surface of mast cells and leukocytes, anaphylactic and anaphylactoid reactions are attributable to a variety of biochemically active amines. These include slow reacting substance of anaphylaxis, eosinophilic chemotactic factor, serotonin, kinins, and prostaglandins (4).

Although histamine, IgE, and complement levels are altered in anaphylactic reactions, to confirm the diagnosis of anaphylaxis one must demonstrate a specific IgE antibody. The classic diagnostic procedure for detecting a reagin-mediated disorder is the skin test, but this may precipitate an adverse response in sensitized patients. Furthermore, skin testing may be positive in the absence of an immunospecific antibody or be negative in patients with proven sensitivity (6). Antigen-specific IgE antibody can be measured by the radioallergosorbent test (RAST) (7, 8).

The RAST is performed by complexing meperidine to an insoluble polymer, then incubating it with the patient's serum. After washing, the amount of IgE antibody to meperidine is determined by further incubation with ^{125}I-labeled anti-IgE. Bound radioactivity reflects meperidine-specific IgE antibody and is compared to a reference system. RAST results are scored by comparison with strongly positive reaginic sera (0, no antibody present; 1, antibody present, very low level; 2, antibody present, low level; 3, antibody present, significant level; 4, antibody present, highly significant level).

RAST has been useful in demonstrating immunospecific IgE to such diverse agents as insulin, hymenoptera extracts, and the penicilloyl derivatives of penicillin (7, 8). The utility of RAST is limited by the requirement of pure antigen, which in the present case was easily obtainable. RAST results have been compared to various provocation tests. Correlations vary from 75% to 100%, depending on the type and the purity of the allergen preparation used and on the degree of hypersensitivity of the patients studied (7, 8). A positive RAST in a healthy nonallergic individual is rare, probably occurring in less than 0.5% of cases (9). The result of the RAST to meperidine with IgE present at a significant level (3+/4+) along with the clinical history confirms the diagnosis of anaphylaxis in our patient.

The treatment of anaphylaxis has been previously reviewed (10). Airway maintenance, oxygen administration, rapid intravascular volume expansion, and epinephrine are the mainstays of therapy. These are necessary to treat the sudden hypotension and hypoxia that result from vasodilation, increased capillary permeability, and bronchospasm. In this case, the dose of epinephrine was excessive for a small child and could potentially have caused further difficulties. Diphenhydramine is probably of minimal value once a reaction occurs, although simultaneously blocking both H_1 and H_2 receptor sites of histamine action (with both diphenhydramine and cimetidine) may be useful (4). Steroids are also of unproven value (10). Seizures that developed in our patient were probably hypoxic in origin and were readily controlled.

In summary, this is the first described report of anaphylaxis to meperidine. This drug and probably other narcotics as well may produce severe idiosyncratic reactions. In addition, this case emphasizes the need to maintain resuscitation equipment and trained personnel whenever drugs of any kind are administered. Previous allergic history is not necessary and is not always obtainable. Anaphylaxis is an acute, potentially fatal reaction but with anticipation, prompt recognition, and adequate treatment a disastrous outcome can be avoided.

REFERENCES

1. Gill C, Michaelides PL. Dental drugs and anaphylactic reactions: report of a case. Oral Surg 1980;50:30–2.
2. Lomtev NG, Ibragimov SI. Anaphylactic shock after premedication with preparations used for performing balanced general anesthesia. Anesteziol Reanimatol 1979;4:62.
3. Vignon H, Gay R, Laxenaire MC. Observations cliniques d'accidents anaphylactoides par et post anesthesique resultat d'enquete a posteriori. Ann Anesthesiol Fr 1976;17:117–9.

4. Watkins J. Anaphylactoid reactions to IV substances. Br J Anaesth 1979;51:51-60.
5. Lowenstein E, Hallowell P, Levine FH, Daggett WM, Austen WG, Laver MB. Cardiovascular response to large doses of morphine in man. N Engl J Med 1969;281:1389-94.
6. Sellow JE, Mendelson LM, Rosen JP. Anaphylactic reaction in skin test-negative patients. J Allergy Clin Immunol 1980;65: 400.
7. Wide L. Clinical significance of measurement of reaginic (IgE) antibody by RAST. Clin Allergy 1973;3:583-95.
8. Johansson SGO, Bennich H, Berg T. The clinical signficance of IgE. Prog Clin Immunol 1972;1:157-81.
9. Berg T, Johansson SGO. Allergy diagnosis with the radioallergosorbent test. J Allergy Clin Immunol 1974;54:209-21.
10. Kelly JF, Patterson R. Anaphylaxis: course, mechanisms and treatment. JAMA 1974;227:1426-31.

Early Bedside Detection of Pulmonary Vascular Occlusion

Bedside balloon occlusion angiography was used to assess the frequency of intravascular occlusive disease in 40 patients suffering acute respiratory failure (ARF). Flow-directed pulmonary artery catheters (Swan-Ganz) were placed at the start of the study. Pulmonary artery filling defects (PAFD) were found in 19 of 40 patients (48%) and were multiple in 15 patients suffering ARF of diverse cause and severity. The PAFD detected 1 to 17 days after endotracheal intubation (median, 2.5 days) had significant correlations ($p < 0.05$) with: (1) the severity of ARF (77% of 13 patients with severe ARF compared with 18% of 11 patients with mild ARF), (2) the presence of disseminated intravascular coagulopathy (DIC) (63% of 19 patients with DIC compared with 33% of 21 patients without DIC), (3) a high pulmonary vascular resistance (PVR) (mean PVR of 2.8 ± 1.7 mm Hg·min/L in patients with PAFD compared with 1.7 ± 1.0 mm Hg·min/L in patients with normal angiograms), and (4) a fatal outcome (63% of 24 patients who died compared with 25% of 16 patients who survived). The mortality rate for patients with multiple PAFD was 93%. Widespread macroscopic and microscopic pulmonary artery thrombi were found in six of seven patients with PAFD and in one of two patients without PAFD among nine patients studied with postmortem barium sulfate gelatin pulmonary artery injections. Necrosis was frequently noted in lung tissue distal to PAFD. The detection of multiple PAFD distal to newly placed Swan-Ganz catheters in patients with ARF indicated severe and potentially fatal lung injury that is likely to be associated with widespread pulmonary artery thrombosis. Bedside balloon occlusion pulmonary angiography, performed early in the course of ARF, can provide a rational anatomic basis for instituting anticoagulant or antithrombic therapy aimed at alleviating vascular occlusive disease and reducing lung damage. *(Greene R, Zapol WM, Snider MT, et al. Early bedside detection of pulmonary vascular occluion during acute respiratory failure. Am Rev Respir Dis 1981;124:593-601)*

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Nitrous Oxide Challenge for Detection of Residual Intravascular Pulmonary Gas following Venous Air Embolism

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Venous air embolism is a potentially dangerous complication of the sitting position as used in neurosurgery. In our experience, multiple episodes of clinically significant pulmonary gas embolism occasionally occur in a patient in whom identification of the site of air entry is difficult. Although continued air entry can usually be prevented by watertight packing of the surgical field, the search for the elusive venous opening cannot proceed during this maneuver. The anesthesiologist must then decide whether the patient's physiologic compensation to the preceding embolic episodes is sufficient to permit further surgical exploration with a high risk of repeated air embolism. The following case report adds another dimension to the management of air embolism as a nitrous oxide challenge was used to aid in detection of residual intravascular pulmonary gas before reinitiation of surgery.

Case Report

A 62-year-old male patient was admitted with a 6-week history of an unsteady gait and "dizziness." Computed tomography scanning revealed a right cerebellar pontine angle mass. The patient's past history included a left pneumonectomy for carcinoma 2 years before admission. His recovery had been unremarkable and there was no evidence of metastasis. He was taking a triamterene-hydrochlorothiazide combination (Dyazide). There was electrocardiogram (ECG) evidence of an old inferior myocardial infarction.

The patient was scheduled for a posterior fossa craniotomy in the sitting position. Customary monitoring protocol for this procedure includes a right atrial catheter, an arterial catheter, Doppler ultrasonic bubble detector, and continuous end-tidal CO_2 analysis (F_{ETCO_2}). Because of the history of a left pneumonectomy and a preoperative chest x-ray, which indicated a leftward shift of mediastinal structures, we felt that positioning of the Doppler probe over the right side of the heart (possibly underlying the sternum) might not be possible. Accordingly, it was decided to replace our standard central venous pressure catheter with a Swan-Ganz (#7 French) catheter with central venous pressure (CVP) and pulmonary arterial pressure (PAP) ports. This was done to enhance the overall sensitivity of methods for detection of air embolism (1). Additional monitors included an ECG, an esophageal stethoscope, and a rectal temperature probe.

Anesthesia was induced with thiopental and maintained with fentanyl, diazepam, pancuronium, and 64% N_2O in oxygen. The patient was secured in the sitting position. Attempts to monitor heart movements with the Doppler to the right of the sternum were unsuccessful. The Doppler probe was then positioned to the left of the sternum in the fourth interspace. In this position the Doppler detected heart movements, although it did not detect cardiac passage of small volumes (0.5 to 1 ml) of CO_2 injected intravenously. Hemodynamic control data gathered at this time are shown in the Table (A). Approximately 30 minutes after the beginning of the operation an abberant venous sinus was entered and air entrainment was simultaneously recognized by the surgeon and by the hemodynamic alterations shown in Fig 1 and the Table (B). This resulted in a slight increase in PAP and was accompanied by a slow decrease in blood pressure (BP) to 130/65 torr but with no change in CVP or F_{ETCO_2}.

Nitrous oxide was discontinued and 2 minutes later as the surgeon attempted to locate the site of air entry a second embolus occurred [Fig 2, Table (C)] leading to arterial hypotension, elevation of CVP, PAP, and a profound decrease in F_{ETCO}.

No change in Doppler tones occurred with either episode, nor was a mill wheel murmur detected. Successful resuscitation efforts included packing the surgical site and intravenous ephedrine (10 mg). No gas could be aspirated from either the CVP or PAP ports of the Swan-Ganz catheter. After approximately 15 minutes, cardiovascular stabilization occurred as indicated in the Table (D).

Twenty minutes after cardiovascular stability was achieved, nitrous oxide (60%) was then administered and 2 minutes later the PAP increased (+5 torr) and the F_{ETCO_2} started to decline in the absence of changes in BP or CVP [Fig 2 and Table (E)]. These alterations were interpreted as indicating residual gas trapped in the lungs. N_2O was again

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Received from the Departments of Anesthesiology and Neurosurgery, Veteran's Administration Hospital, La Jolla, California, and University of California at San Diego, La Jolla, California. Accepted for publication November 10, 1981.
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TABLE

Hemodynamic and End-tidal CO_2 Data*

	BP	$\overline{CVP}$	PAP	FET_{CO_2}
		torr		%
A. Control	150/90	7	23/16	5.0
B. First embolus	130/65	3	25/20	5.0
C. Second embolus	50/30	10	43/35	0.9
D. Postresuscitation	100/55	3	25/20	4.4
E. First N_2O test administration	100/55	3	31/25	3.9
F. After N_2O test	105/60	3	21/18	4.0
G. Second N_2O test	90/50	3	22/18	3.9

* Abbreviations used are: BP, arterial blood pressure; $\overline{CVP}$, mean central venous pressure; PAP, pulmonary arterial pressure; FET_{CO_2}, end-tidal CO_2.

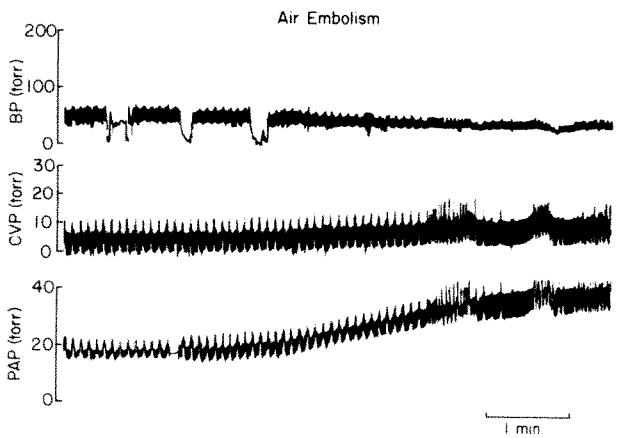


FIG 1. Effect of venous air embolism on arterial blood pressure (BP), central venous pressure (CVP), and pulmonary arterial pressure (PAP).

discontinued. Twenty minutes later the 60% N_2O challenge was repeated with no changes in PAP or FET_{CO_2} and surgery continued using halothane and an FI_{O_2} of more than 98% [Table (G)].

During attempts to control bleeding from the venous sinus, 1500 ml of blood was lost and five additional episodes of air embolism occurred despite compression of the internal jugular veins and positive expiratory pressure. During each episode, PAP increased dramatically and FET_{CO_2} decreased. At no time was the precordial Doppler effective in detecting intravascular gas. Air was aspirated successfully on four occasions. After each episode the wound was packed and the patient allowed to return to near base line physiologic indices before resumption of surgery. The N_2O challenges were used following each episode to aid in determining when surgery could resume. Once venous hemorrhage was controlled, the wound was closed and the procedure terminated with the plan in mind of returning at a later date for a definitive surgical procedure. Arterial blood gases showed good oxygenation throughout surgery. The Pa_{CO_2} increased following the air emboli from 39 torr

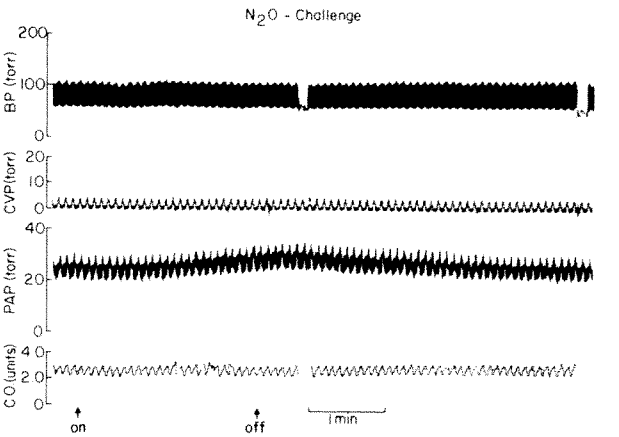


FIG 2. Effect of 60% N_2O administration (↑ = on, ↓ = off) on BP, CVP, PAP, and cardiac output (CO) 20 minutes after massive air embolism.

to a high of 59 torr despite increasing minute ventilation from 6.4 to 8.6 L/min. The Pa_{CO_2} returned slowly to normal following resolution of the episode.

The patient remained intubated overnight while being ventilated with intermittent mandatory ventilation. During weaning from the ventilator arterial blood gas tensions remained within normal limits and the patient was extubated the following morning. Postoperative chest x-rays showed indistinct pulmonary vasculature compatible with interstitial edema. Recovery was uncomplicated and 1 week later the procedure was completed in the prone position.

Discussion

Among the methods designed to detect venous air embolism, FET_{CO_2} analysis and PAP measurement provide a semiquantitative estimate of the volume of the embolus and its rate of dissipation from the distal pulmonary vasculature (1, 2). These qualities, when combined with a N_2O challenge in apparently stabilized patients following air embolisms, can sharpen the anesthesiologist's ability to time resumption and extent of additional high risk surgery. Where repeated embolism is likely, maximal compensation from the prior embolic episode should be attained before the patient is again placed at risk.

In our patient N_2O was deleted from the anesthetic technique following the first air embolism. However, N_2O was briefly reintroduced (60% N_2O for 5 minutes) as a challenge to detect residual possible gas in the pulmonary vascular tree after PAP had returned to preembolism base line levels during inspiration of 100% halothane in oxygen. Following the second and massive air embolism, the N_2O challenge 35 minutes after embolism had occurred was positive, with increases in PAP of approximately 5 torr and decreases

in F_{ETCO_2}. Absence of an increase in PAP or decrease in F_{ETCO_2} to a N_2O test was interpreted as a sign that pulmonary excretion of intravascular air was virtually complete. The test became negative after 65 minutes and surgery resumed. Following two subsequent episodes of air embolism, the test was negative after 8 and 10 minutes, respectively. These episodes were characterized by only small volumes of gas embolized to the lungs. Under controlled conditions, the N_2O test for residual intravascular pulmonary gas can be safely performed and provide important physiologic insight. However, we are not suggesting that N_2O be continuously administered following a clinically significant episode of air embolism.

Intermittent use of 80% N_2O in combination with measurement of PAP and F_{ETCO_2} as a diagnostic test to detect early asymptomatic air embolism has been suggested by Munson et al (3). In their case report N_2O was administered for up to 8 minutes and elevations in PAP greater than those observed in our patient occurred. This may have been due to their use of higher N_2O concentrations, more prolonged administration of N_2O, or higher volumes of residual intravascular lung gas. Our suggested application of the N_2O test requires that an elevation of PAP more than 5 torr should be immediately followed by discontinuation of N_2O to prevent possible precipitation of adverse physiologic consequences. In the patient of Munson et al PAP remained high despite withdrawal of N_2O after a net increase of +14/+6 torr. We agree with Munson et al (3) that the intermittent administration of N_2O while measuring PAP and F_{ETCO_2} in patients with suspected retained intravascular pulmonic gas is a useful diagnostic adjunct. It can be especially helpful in deciding when lung excretion of intravascular air is essentially complete.

REFERENCES

1. English JB, Westenskow D, Hodges MR, Stanley TH. Comparison of venous air embolism monitoring in supine dogs. Anesthesiology 1978;48:425–9.
2. Vestappen FTJ, Bernads JA, Kreuzer F. Effects of pulmonary gas embolism on circulation and respiration in the dog. III. Excretion of venous bubbles by the lung. Pfluegers Arch 1977;370:67–70.
3. Munson ES, Paul WL, Perry JC, et al. Early detection of venous air embolism using a Swan-Ganz catheter. Anesthesiology 1975;42:223–6.

Ventricular Distention during Postischemic Reperfusion

To assess the effects of left ventricular distention during the early reperfusion period following ischemic arrest, 16 canine heart preparations were subjected to 45 minutes of hypothermic (27°C) cardioplegia arrest and normothermic reperfusion. Isovolumic left ventricular developed pressure and rate of rise of left ventricular pressure (dP/dt) were measured with an intraventricular balloon; endocardial/epicardial flow ratios were determined with microspheres; and myocardial gas tensions were monitored using mass spectrometry. During early reperfusion, group 1 hearts (n = 8) were not distended (end-diastolic pressure = 0). Group 2 hearts (n = 8) were subjected to an end-diastolic pressure of 20 mm Hg for the initial 15 minutes of reperfusion. Group 2 hearts demonstrated impaired subendocardial blood flow after 5 minutes of reflow (0.75 ± 0.06 vs 0.96 ± 0.04, endocardial/epicardial flow rates, group 2 vs group 1) and persistent elevation of intramyocardial carbon dioxide tension (68 ± 4 vs 51 ± 4 mm Hg, group 2 vs group 1). In addition, postischemic ventricular function was significantly worse in group 2 hearts (60 ± 7% vs 79 ± 3% of control dP/dt, group 2 vs group 1, and 53 ± 6% vs 81 ± 5% of control left ventricular developed pressure, group 2 vs group 1). These data demonstrate that even mild distention during early reperfusion can result in reduced subendocardial perfusion and delayed washout of tissue CO_2. Although myocardial blood flow and CO_2 tension subsequently returned to normal in the distended hearts, left ventricular performance remained significantly depressed. This injury can occur clinically in nonvented hearts prior to the resumption of effective ventricular contraction. *(Lucas SK, Schaff HV, Flaherty JT, Gott VL, Gardner TJ. The harmful effects of ventricular distention during postischemic reperfusion. Ann Thorac Surg 1981;32:486–94).*

letters TO THE EDITOR

Aminophylline

To the Editor:

The recent review of aminophylline by Stirt and Sullivan (1) was of interest. The authors correctly state that the beneficial effects of this drug in the treatment of airflow obstruction are mediated not only via the inhibition of phosphodiesterase, but also by catecholamine release and effects on extracellular calcium concentration. They neglect to mention, however, the potentially important influence of aminophylline on diaphragmatic contractility.

Aubier et al (2) have clearly shown that aminophylline causes a marked increase in diaphragmatic contractility. Aminophylline has been shown not to alter the mechanics of normal human lung (3). Furthermore, in a recent study of asthmatic patients, the improvement in airflow obstruction after aminophylline treatment could not be correlated with serum aminophylline levels (4).

Aminophylline may exert its crucial therapeutic effect, not via bronchodilation, but rather by its ability to increase the contractility of the respiratory muscles.

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REFERENCES

1. Stirt J, Sullivan S. Aminophylline. Anesth Analg 1980;60:587-602.
2. Aubier M, DeTroyer A, Sampson M, MacKlem PT, Roussos C. Aminophylline improves diaphragmatic contractility. N Engl J Med 1981;305:249-52.
3. Estenne M, Yernault J-C, DeTroyer A. Effects of parenteral aminophylline on lung mechanics in normal man. Am Rev Respir Dis 1980;121:967-71.
4. Rossing TH, Fanta CH, Goldstein DH, Snapper JR, McFadden ER Jr. Emergency therapy of asthma: comparison of the acute effects of parenteral and inhaled sympathomimetics and infused aminophylline. Am Rev Respir Dis 1980;122:365-71.

To the Editor:

We thank Dr. Rosko for his comments on our recent article (1). As he points out, the therapeutic efficacy of aminophylline in asthma may stem from other, less widely appreciated actions than simply bronchodilation. For example, competitive inhibition by aminophylline of adenosine, a purine linked to the sugar ribose and distributed ubiquitously throughout the body, has been reported to antagonize histamine release (2). Nevertheless, relaxation of airway smooth muscle by aminophylline has been demonstrated (3). It is interesting to find that both smooth muscle relaxation and skeletal (diaphragmatic) muscle contractility (4) are enhanced by aminophylline. A drug may have markedly different effects in different tissues.

As noted by Dr. Rosko, a recent study in asthmatic patients (5) demonstrated no correlation of serum theophylline levels with improvement in airway function, yet another report (6) has shown a definite improvement in ventilatory function in asthmatic patients that is well correlated with serum theophylline levels. Both studies utilized intravenous aminophylline doses which produced serum theophylline levels in the therapeutic range (10 to 20 mg/L) (7). Why, then, were opposite results obtained?

Of the utmost importance in considering the effects of aminophylline, or any drug or therapeutic maneuver, is the clinical setting in which it is used. In one of the above studies (5), aminophylline was administered during asthmatic episodes in the emergency room; in the second (6), the drug was administered to already hospitalized patients following an asthmatic attack. Thus, it might be fairly concluded from the apparently contradictory results that in a quiescent patient, recovering from an acute asthmatic episode, aminophylline may be beneficial in proportion to the circulating serum theophylline level, whereas in an acutely bronchospastic patient in an emergency room setting, other therapeutic modalities might be more efficacious.

Of course, these conclusions must be tempered by the realization that during asthmatic episodes, "the amount of discomfort or dyspnea that a patient perceives varies greatly and sometimes correlates poorly with objective measures of airway obstruction. Wheezing may be present when obstruction and even discomfort are minimal, and may be absent when obstruction is severe (8)." In few other medical conditions is the psychological background and conscious input as important in initiating, perpetuating, and resolving the problem. In this regard, recent evidence that aminophylline may enhance respiratory function by cerebral dopamine receptor activation (9) indicates that much remains to be learned about the mechanisms of action of aminophylline.

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REFERENCES

1. Stirt JA, Sullivan SF. Aminophylline. Anesth Analg 1981;60:587-602.
2. Marquardt DL, Parker CW, Sullivan TJ. Potentiation of mast cell mediator release by adenosine. J Immunol 1978;120:871-8.
3. Niewoehner DE, Campe H, Duane S, McGowan T, Montgomery MR. Mechanisms of airway smooth muscle response to isoproterenol and theophylline. J Appl Physiol 1979;47:330-6.
4. Aubier M, DeTroyer A, Sampson M, MacKlem PT, Roussos C. Aminophylline improves diaphragmatic contractility. N Engl J Med 1981;305:249-52.

5. Rossing TH, Fanta CH, Goldstein DH, Snapper JR, McFadden ER Jr. Emergency therapy of asthma: comparison of the acute effects of parenteral and inhaled sympathomimetics and infused aminophylline. Am Rev Respir Dis 1980;122:365-71.
6. Mitenko PA, Ogilvie RI. Rational intravenous doses of theophylline. N Engl J Med 1973;289:600-3.
7. Piafsky KM, Ogilvie RI. Dosage of theophylline in bronchial asthma. N Engl J Med 1975;292:1218-22.
8. Franklin W. Asthma in the emergency room. N Engl J Med 1981;305:826-7.
9. Lundberg DB, Breese GR, Mueller RA. Aminophylline may stimulate respiration in rats by activation of dopaminergic receptors. J Pharmacol Exp Ther 1981;217:215-21.

Nitrous Oxide and Swan-Ganz Catheters

To the Editor:

Kaplan, Abramowitz, and Epstein (1) have recently demonstrated that inflation of a Swan-Ganz catheter balloon with air is followed by a further expansion of the balloon when exposed to an atmosphere containing nitrous oxide. Being interested in a possible relationship between overdistention of the balloon and the morbidity of Swan-Ganz catheterization, we too have studied this phenomenon.

We studied five #7 French Swan-Ganz catheters (Edwards Laboratories, Santa Ana, CA). We used gas-equilibrated saline at 37°C rather than a gaseous medium to surround the balloon as we had previously observed that equilibration is affected by this difference. We chose saline because it most closely mimicked in vivo conditions. Also, we used 1.5 ml as the balloon inflation volume (as recommended by Edwards Laboratories) because we found that injection of 1.0 ml (as used by Kaplan et al) did not always result in balloon inflation.

Our results (Table, Fig 1) differ quantitatively from those of Kaplan et al (1). They found near maximum volume changes occurred between 5 to 10 minutes, whereas we found that the balloons were still expanding rapidly at 10 minutes. The difference in experimental conditions probably accounts for the slower rate of change observed by us.

Edwards Laboratories recommends that filtered CO_2 be used for inflating the balloon "because of its rapid absorption into the blood should the balloon rupture within the circulation." They state that CO_2 diffuses through the balloon, reducing its volume at a rate of approximately 0.5 ml/min (Swan-Ganz catheter package insert, Edwards Laboratories). We studied the effects of inflating the balloons with 1.5 ml of 100% CO_2 and exposing them to saline equilibrated with 50% and 75% N_2O. Our findings (Fig 2) indicate that the rate of volume decrease is much less if the surrounding medium contains N_2O than if it contains air.

When the balloons were inflated with 1.5 ml of the same N_2O mixture as was used for saline equilibration, volume decreased with time in all balloons. The rate was greater with 75% N_2O than with 50% N_2O, but slower than when the balloons were inflated with 100% CO_2 (Table). If

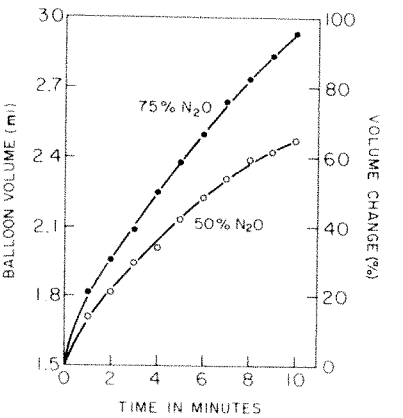


FIG 1. Changes in balloon volume, with time, when inflating gas is air (1.5 ml) and surrounding medium is nitrous oxide in saline.

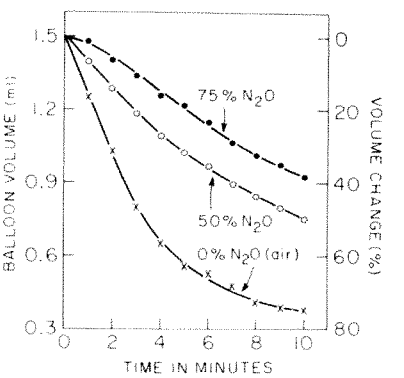


FIG 2. Changes in balloon volume, with time, when inflating gas is 100% carbon dioxide (1.5 ml) and surrounding medium is nitrous oxide in saline or air in saline.

TABLE

Change in Balloon Volume*

Inflating gas (unit of change)	Air		Gas in surrounding saline 50% N_2O		75% N_2O	
	5 min	10 min	5 min	10 min	5 min	10 min
Air						
ml	−0.02 ± 0.02	−0.03 ± 0.05	0.64 ± 0.07	0.98 ± 0.04	0.88 ± 0.13	1.44 ± 0.19
%	−1 ± 1	−2 ± 3	42 ± 5	65 ± 3	58 ± 9	96 ± 13
50 % N_2O						
ml	—	—	−0.14 ± 0.05	−0.27 ± 0.15	—	—
%	—	—	−9 ± 3	−18 ± 10	—	—
75% N_2O						
ml	—	—	—	—	−0.25 ± 0.05	−0.44 ± 0.12
%	—	—	—	—	−17 ± 3	−29 ± 8
100% CO_2						
ml	−0.97 ± 0.13	−1.12 ± 0.21	−0.47 ± 0.13	−0.74 ± 0.20	−0.31 ± 0.05	−0.57 ± 0.16
%	−63 ± 9	−75 ± 14	−32 ± 9	−50 ± 13	−18 ± 3	−38 ± 11

* Values are means ± SD. Inflating gas volume of 1.5 ml at 0 minutes, saline at 37°C.

deflation of the balloon during passage into the pulmonary artery allows exposure of the catheter tip, which may traumatize the heart or lungs, then a slower rate of volume decrease provides greater safety.

We found that the pressure required to inflate the balloons to 1.5 ml varied from 100 to 250 torr indicating a wide range of compliance. Three highly compliant balloons expanded rapidly and ruptured before 10 minutes when inflated with air and exposed to 75% N_2O. Trauma resulting from unrecognized balloon expansion or pressure increase is therefore a real possibility. Indeed, Barash et al (2) have recently suggested that a pressure release mechanism be incorporated into the balloon inflation port so that inadvertent high pressure cannot be obtained.

We conclude that for the patient anesthetized with nitrous oxide, it is desirable from all points of view, to inflate the balloon with either the respired gas mixture, or with 100% CO_2.

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REFERENCES

1. Kaplan R, Abramowitz MD, Epstein BS. Nitrous oxide and air-filled balloon-tipped catheters. Anesthesiology 1981;55:71-3.
2. Barash PG, Nardi D, Hammond G, et al. Catheter-induced pulmonary artery perforation. J Thorac Cardiovasc Surg 1981;82:5-12.

Difficult Spinal Taps

To the Editor:

The method of approaching the subarachnoid space in difficult situations as described by Abboud (1) is not entirely new or novel. Lund (2) for years taught this approach, which he termed "sublaminar," and described this technique in his book on spinal anesthesia. This is an excellent approach in any situation, but especially in the patient who for whatever reason cannot flex his/her spine.

Lund's approach was to make the skin wheal 1.5 to 2.0 cm lateral to the midline with the needle angled at 30 to 45 degrees.

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REFERENCES

1. Abboud TK. An easy approach for difficult spinal anesthesia in the parturient. Anesth Analg 1981;60:770.
2. Lund PC. Principles and practice of spinal anesthesia. Springfield, IL: Charles C Thomas, 1971.

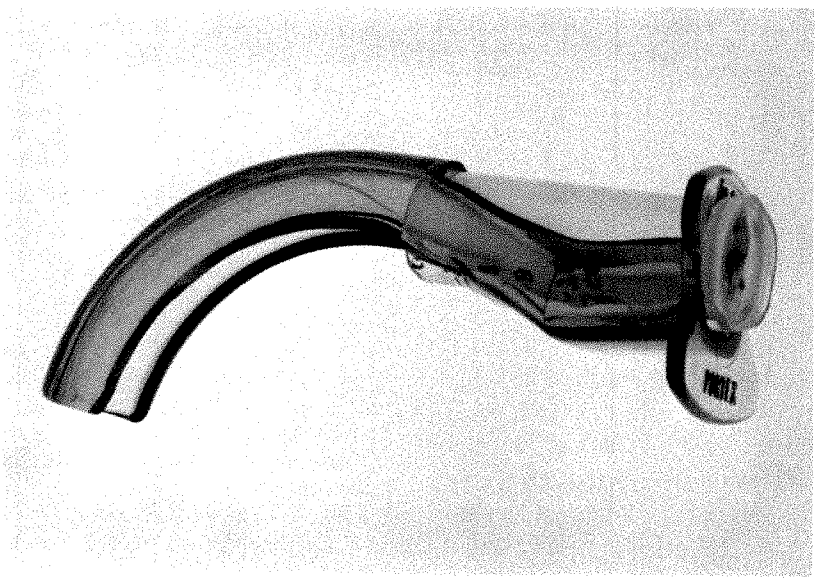


FIGURE. Oblique view of prototype of airway intubator.

Airway Intubator

To the Editor:

We read Vredovoe's description (1) of a slotted oropharyngeal airway as an aid to fiberoptic orotracheal intubation with interest. One disadvantage of the technique described is that the slotted airway must be withdrawn and removed before the endotracheal tube can be passed distally over the bronchoscope. This is because the lumen of a 10-cm oropharyngeal airway (Portex) is oval in cross section and measures 7 mm x 16 mm. We solved this problem (for different reasons) by (*a*) cutting wide slots from the underside distally and the upper side proximally, and (*b*) making the bite area circular in cross section by using part of the barrel of a 10-ml syringe (Figure). This airway intubator (2), now available commercially, was designed to be both an oropharyngeal airway and, should the need arise, a guide for oral intubation as a well curved plastic endotracheal tube can be passed through the proximal half, which acts as a splint, into the distal half which acts as a guide, and thence into the trachea. Intubations using this device have been successfully accomplished in unusual positions (3) and also in situations when intubation with a laryngoscope had been impossible.

An airway intubator would seem to fulfill Vredovoe's requirements with the added advantage that intubation could immediately be carried out through the airway-intubator as the bronchoscope enters the trachea.

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REFERENCES

1. Vredevoe LA, New Techniques for fiberoptic intubation and laryngeal examination. Anesth Analg 1981;60:617.
2. For intubation in a hurry (editorial). Emer Med 1981;13:122.
3. Williams RT, Harrison RE. Prone tracheal intubation simplified using an airway intubator. Can Anaesth Soc J 1981;28:288.

book REVIEWS

Anesthesia and the Obese Patient: Contemporary Anesthesia Practice, Volume 5, edited by B. R. Brown, Philadelphia, F. A. Davis Co., 1981, 139 pp, $22.00.

Most clinically oriented anesthesiologists have come to recognize that treatment of the obese patient involves significant risk factors which are challenging and sometimes annoying. These anesthesiologists are challenged by the many technical variations required to administer a safe anesthetic and annoyed by the mystique and sometimes irreverence surrounding the "fat one."

Dr. Brown and the five contributing authors have succeeded in explaining some of the differences between obesity and morbid obesity, and reviewing at least one of the basic metabolic processes contributing to the condition, i.e., liver metabolism in obesity. In addition, the cardiopulmonary pathophysiology associated with the problem has been reviewed. The obese patient is indeed different.

The chapter on liver metabolism in obesity is informative, relating much of the present fund of knowledge available on this subject. Its brevity demands careful and thoughtful absorption of its contents, but the references will enable the reader to pursue whichever aspect of the problem seems to him/her of greater interest.

One chapter deals with biochemical and biotransformation derangements in the obese patient. Because the "fatty liver" does not work in quite the same way as the normal one, the clinician needs to review what is known at the present time in order to select an appropriate volatile or injectable agent.

The review of the pulmonary and cardiovascular derangements is quite extensive, and most of the abnormal findings are presented along with their implications to the anesthesiologist and to the safety of the patient. The important "abnormal numbers" associated with the evaluation of these systems are given with direct reference to the complications that may be incurred unless preventative measures are taken. There is a direct correlation made with this information in the chapter on intra-anesthetic and postanesthetic ventilation problems. All of the important references on the depression of ventilation by anesthesia and surgery are given. Thus, the anesthesiologist is prepared to educate his surgical colleague with specific data explaining the aggressive postanesthetic support of cardiorespiratory function, particularly the latter.

This reviewer was disappointed by the lack of attention to the techniques of securing and protecting the airway. Information on the use or abuse of postoperative mechanical ventilation is also lacking. Dr. Brown seemed to promise its inclusion at one point, but it never occurred in print.

There are chapters on the surgical techniques used to counteract obesity, and there are data that evaluate the success or failure of the several techniques that are used. The postoperative physiologic derangements caused by these surgical procedures are important for the anesthesiologist's evaluation when one of these patients is seen for anesthesia for other surgical procedures.

The chapter, "Effects of Massive Weight Loss," represents a compilation of data obtained during the first year following such surgery, including psychological and psychiatric changes that may be seen. Some patients were observed for as long as 3 years.

Included for completeness is a chapter on nursing care for the severely obese patient. The information is needed by the anesthesiologist who must/should plan total support for such patients; many practical problems of patient care, provided by nursing and other hospital personnel, are outlined and solutions proposed.

The obese and morbidly obese patient deserves better treatment than anesthesiologists have been able to provide thus far. This well written book provides important data that will improve our care of such patients. I recommend this book for all anesthesiologists, especially those who see such patients on an occasional and usually totally unexpected basis.

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Introduction to Medical Hypnosis, by B. H. Gorsky and S. R. Gorsky, Garden City, NY, Medical Examination Publishing Co., Inc., 1981, 215 pp, $25.00 hardbound, $16.00 paperback.

The authors of this small book dedicate it to "Black Cats of all Colors." This intriguing dedication is

followed by a well written discussion of the nature of hypnosis, a brief history of hypnosis, and an attempt to highlight myths related to hypnosis which are found in the literature. Approximately one third of the book is devoted to these fascinating subjects. The chapter on the history of hypnosis is especially intriguing because the authors have condensed a large body of knowledge into a short and accurate chapter concerning this fascinating aspect of the subject. The junior author is an Associate Professor of English, and I suspect she has contributed a significant amount of the data concerning not only the history of hypnosis, but also information concerning myths about hypnosis as portrayed in classical literature. This portion of the book is well done.

Discussions in subsequent chapters pertaining to hypnotic induction and the trance phenomena, although well written, do not give specific instructions for the beginner who is interested in hypnosis. Perhaps this is good because hypnosis should not be a self-taught discipline. Brief discussions of the use of hypnosis for various medical and psychological problems are given. I was disappointed that the discussion of the use of hypnosis for both acute and chronic pain is quite brief. However, the authors do note the limitations of the use of hypnosis for the treatment of pain as well as the other clinical syndromes that they discuss. It is important to note that the authors do not emphasize the all-inclusive use of hypnosis as many authors do. They discuss the use of hypnosis in habit modification for smoking and dieting but do not give information concerning the efficacy of such treatment for these conditions.

This book is not a definitive work on medical hypnosis, and the authors note this by referring to their work as an "introduction" to medical hypnosis. One of the strong points of the book is a large section on suggestions for further reading in the subject. The book is a good introductory view of medical hypnosis, but should not be construed as a pragmatic text.

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Problems in Anesthesia: A Case Study Approach, by M. B. Ravin, Boston, Little, Brown and Co., 1981, 259 pp, $14.95.

Dr. Ravin and co-authors have created an introductory text with an interesting form of presentation. The book is admittedly written for those with the clinical expertise and knowledge of a third year medical student. In general, the authors have concentrated their discussion on the most common occurrences in an anesthesiologist's practice. Several chapters such as "Pathophysiology and Treatment of Shock," "Anesthesia for the Patient with Renal Disease," and "Reflex Sympathetic Dystrophy" have delved more deeply into the subject matter and provide interesting material for even the experienced anesthesiologist.

The format of this book provides a captivating yet informative means for presenting some basic material. The author uses this form in a fairly uniform manner. Each of the 18 chapters begins with a short philosophic introduction to the subject matter followed by a case report, which includes problem solving and complications that illustrate the chapter's points of interest. Most of the case reports are concise and simple, although a few are wordy with inclusion of some nonpertinent information. Each case report includes a history, physical examination results, and preoperative, intraoperative, and postoperative management. The case report is then followed by a short set of questions, which locks the following discussion to the salient points of the case report. Although basic, this discussion presents a concise, well organized approach to the subject matter. Finally, a summary finishes each chapter by emphasizing the high points of the discussion.

The subject matter itself varies from some very basic disorders (apnea, hypocarbia, hypercarbia, hypotension, hypertension) to somewhat more complicated areas of anesthetic patient management (patients with renal disease, cardiovascular disease, asthma, and myasthenia, and pediatric patients). Other general areas included are: pharmacology of local anesthetics, pathophysiology and treatment of shock, and reflex sympathetic dystrophy. Although many areas of anesthesia are covered in a nonsequential manner, this book in no way presents a complete study of the practice of the anesthesiologist.

The book, second only to the clinical setting, successfully accomplishes the first purpose of the author, that being "to teach the student about the thought processes of the anesthesiologist." The second purpose, "to demonstrate how the practice of anesthesia is the practice of medicine," remains self-evident throughout the book. Although the utilization of the case study approach provides an interesting way of introducing the student to the practice of anesthesia, its nonsequential manner requires that it be presented along with a more standard text. Despite its lack of completeness, this book offers much to the new anesthesia student and the reviewer believes it well worth reading.

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BOOKS RECEIVED

International Anesthesiology Clinics: Occupational Hazards to Operating Room and Recovery Room Personnel, Volume 19, edited by J. E. Cottrell, Boston, Little, Brown & Co, Winter 1981, 183 pp, $40.00/yr.

Ethics and Regulation of Clinical Research, by R. J. Levine, Baltimore, Urban & Schwarzenberg, 1981, 299 pp, $35.00.

Ambulatory Health Services in America: Past, Present, and Future, by M. I. Roemer, Rockville, MD, Aspen Systems Corp, 1981, 468 pp, $33.50.

Handbook of Percutaneous Central Venous Catheterisation, by M. Rosen, I. P. Latto, and W. Shang, Philadelphia, WB Saunders, 1981, 134 pp, $28.00.

A Guide for Authors

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Illustrations must be good quality, unmounted glossy prints, usually 12.7 by 17.3 cm (5 by 7 in), but no larger than 20.3 by 25.4 cm (8 by 10 in).

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Books and Other Monographs

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   Rhodes AJ, Van Rooyen CE, comps. Textbook of virology: for students and practitioners of medicine and the other health sciences. 5th ed. Baltimore: Williams & Wilkins, 1968.

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   Weinstein L, Swartz MN. Pathogenic properties of invading microorganisms. In: Sodeman WA Jr, Sodeman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: WB Saunders, 1974:457-72.

7. Agency Publication

   National Center for Health Statistics. Acute conditions: incidence and associated disability, United States July 1968-June 1969. Rockville, Md.: National Center for Health Statistics, 1972. (Vital and health statistics. Series 10: Data from the National Health Survey, no. 69) (DHEW publication no. (HSM)72-1036).

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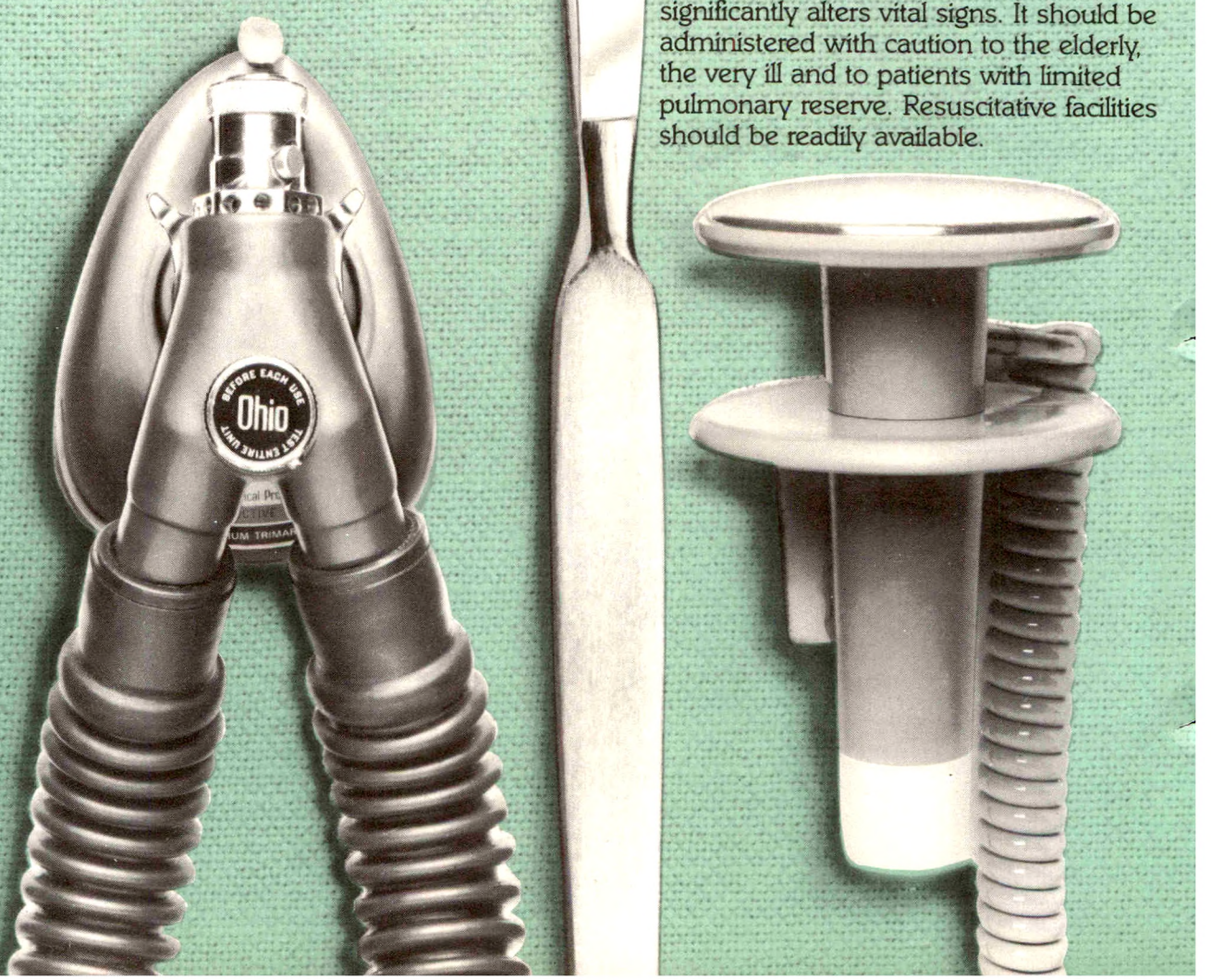
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Injectable Valium (diazepam/Roche), administered intramuscularly approximately one hour before surgery, produces the antianxiety response you want. Patients, though calmer, typically remain well-oriented and able to cooperate. When an amnesic effect is desired, intravenous administration just prior to anesthesia produces diminished recall of unpleasant aspects of the induction period. (The dosage of concomitant narcotic analgesics should be reduced by at least one third and in some cases may be omitted.) Since it requires no reconstitution, Injectable Valium is ready immediately.

Pre-procedure

Excessive anxiety in patients facing such procedures as endoscopy or cardioversion can be relieved almost immediately by administering Injectable Valium (diazepam/Roche) I.V. Peak blood levels and expected clinical response are usually achieved in less than 3 minutes. Most patients are greatly relaxed, yet alert enough to respond to directions. And Valium provides the added advantage of predictable anterograde amnesia: usually lasting only 20 to 60 minutes, in sharp contrast to agents producing amnesia for up to 8 hours—sometimes longer. Used appropriately, Injectable Valium seldom significantly alters vital signs. It should be administered with caution to the elderly, the very ill and to patients with limited pulmonary reserve. Resuscitative facilities should be readily available.



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Post-op

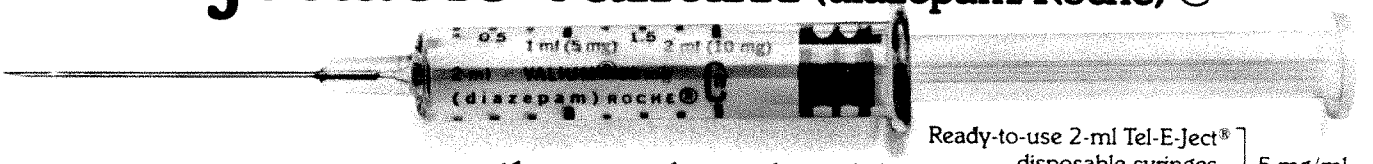
Offering I.M. or I.V. dosage options, Injectable Valium (diazepam/Roche) can be especially useful in patients who cannot take medication by mouth during the postoperative period. Its pronounced calming action relieves the excessive anxiety that can not only complicate the recovery process, but often intensifies pain perception. Used adjunctively, Injectable Valium also helps to relieve painful skeletal muscle spasm, frequently seen in the postsurgical patient.

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Injectable Valium® (diazepam/Roche) Ⓥ



Ready-to-use 2-ml Tel-E-Ject® disposable syringes
2-ml ampuls, 10-ml vials
} 5 mg/ml

versatile...and predictable

- prompt control of anxiety/apprehension
- anterograde amnesia of brief duration
- effective adjunctive skeletal muscle relaxant
- useful in outpatients as well as inpatients

Please consult complete product information, a summary of which follows:

Indications: Management of anxiety disorders, or short-term relief of symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic. Symptomatic relief of acute agitation, tremor, impending or acute delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in: relief of skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; tetanus; status epilepticus, severe recurrent seizures; adjunctively in anxiety, tension or acute stress reactions prior to endoscopic/surgical procedures; cardioversion.

Contraindications: Hypersensitivity; acute narrow angle glaucoma; may be used in paitents with open angle glaucoma receiving appropriate therapy.

Warnings: *To reduce the possibility of venous thrombosis, phlebitis, local irritation, swelling, and, rarely, vascular impairment when used I.V.: inject slowly, taking at least one minute for each 5 mg (1 ml) given; do not use small veins, i.e., dorsum of hand or wrist; use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute Valium (diazepam/Roche) with other solutions or drugs in syringe or infusion flask. If it is not feasible to administer Valium directly I.V., it may be injected slowly through the infusion tubing as close as possible to the vein insertion.*

Administer with extreme care to elderly, very ill, those with limited pulmonary reserve because of possibility of apnea and/or cardiac arrest; concomitant use of barbiturates, alcohol or other CNS depressants increases depression with increased risk of apnea; have resuscitative facilities available. When used with narcotic analgesic, eliminate or reduce narcotic dosage at least ⅓, administer in small increments. Should not be administered to patients in shock, coma, acute alcoholic intoxication with depression of vital signs. As with most CNS-acting drugs, caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).

Has precipitated tonic status epilepticus in patients treated for petit mal status or petit mal variant status.

Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation after long use of excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after long, continuous use at high therapeutic levels. After extended therapy, gradually taper dosage.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations, as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Not recommended for OB use.

Efficacy/safety not established in neonates (age 30 days or less); prolonged CNS depression observed. In children, give slowly (up to 0.25 mg/kg over 3 minutes) to avoid apnea or prolonged somnolence; can be repeated after 15 to 30 minutes. If no relief after third administration, appropriate adjunctive therapy is recommended.

Precautions: Although promptly controlled, seizures may return; readminister if necessary; not recommended for long-term maintenance therapy. If combined with other psychotropics or anticonvulsants, carefully consider individual pharmacologic effects—particularly with known compounds which may potentiate action of Valium (diazepam/Roche), *i.e.*, phenothiazines, narcotics, barbiturates, MAO inhibitors, antidepressants. Protective measures indicated in highly anxious patients with accompanying depression who may have suicidal tendencies. Observe usual precautions in impaired hepatic function; avoid accumulation in patients with compromised kidney function. Laryngospasm/increased cough reflex are possible during peroral endoscopic procedures; use topical anesthetic, have necessary countermeasures available. Hypotension or muscular weakness possible, particularly when used with narcotics, barbiturates or alcohol. Use lower doses (2 to 5 mg) for elderly/debilitated.

The clearance of Valium and certain other benzodiazepines can be delayed in association with Tagamet (cimetidine) administration. The clinical significance of this is unclear.

Adverse Reactions: Drowsiness, fatigue, ataxia, venous thrombosis/phlebitis at injection site, confusion, depression, dysarthria, headache, hypoactivity, slurred speech, syncope, tremor, vertigo, constipation, nausea, incontinence, changes in libido, urinary retention, bradycardia, cardiovascular collapse, hypotension, blurred vision, diplopia, nystagmus, urticaria, skin rash, hiccups, changes in salivation, neutropenia, jaundice. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Cough, depressed respiration, dyspnea, hyperventilation, laryngospasm/pain in throat and chest have been reported in peroral endoscopic procedures. Isolated reports of neutropenia, jaundice; periodic blood counts, liver function tests advisable during long-term therapy. Minor EEG changes, usually low-voltage fast activity, of no known significance.

Dosage: Usual initial dose in older children and adults is 2 to 20 mg I.M. or I.V., depending on indication and severity. Larger doses may be required in some conditions (tetanus). In acute conditions injection may be repeated within 1 hour, although interval of 3 to 4 hours is usually satisfactory. Lower doses (usually 2 to 5 mg) with slow dosage increase for elderly or debilitated patients and when sedative drugs are added. (See Warnings and Adverse Reactions.)

For dosages in infants and children see below; have resuscitative facilities available.

I.M. use: by deep injection into the muscle.

I.V. use: inject slowly, take at least one minute for each 5 mg (1 ml) given. Do not use small veins, i.e., dorsum of hand or wrist. Use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute Valium (diazepam/Roche) with other solutions or drugs in syringe or infusion flask. If it is not feasible to administer Valium directly I.V., it may be injected slowly through the infusion tubing as close as possible to the vein insertion.

Moderate anxiety disorders and symptoms of anxiety, 2 to 5 mg I.M. or I.V. and severe anxiety disorders and symptoms of anxiety, 5 to 10 mg I.M. or I.V., repeat in 3 to 4 hours if necessary; acute alcoholic withdrawal, 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary. Muscle spasm, in adults, 5 to 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary (tetanus may require larger doses); in children, *administer I.V. slowly;* for tetanus in infants over 30 days of age, 1 to 2 mg I.M. or I.V., repeat every 3 to 4 hours if necessary; in children 5 years or older, 5 to 10 mg repeated every 3 to 4 hours as needed. Respiratory assistance should be available.

Status epilepticus, severe recurrent convulsive seizures (I.V. route preferred), 5 to 10 mg adult dose administered slowly, repeat at 10- to 15-minute intervals up to 30 mg maximum. Repeat in 2 to 4 hours if necessary keeping in mind possibility of residual active metabolites. Use caution in presence of chronic lung disease or unstable cardiovascular status. Infants (over 30 days) and children (under 5 years), 0.2 to 0.5 mg slowly every 2 to 5 min., up to 5 mg (I.V. preferred). Children 5 years plus, 1 mg every 2 to 5 min., up to 10 mg (slow I.V. preferred); repeat in 2 to 4 hours if needed. EEG monitoring may be helpful.

In endoscopic procedures, titrate I.V. dosage to desired sedative response, generally 10 mg or less but up to 20 mg (if narcotics are omitted) immediately prior to procedure; if I.V. cannot be used, 5 to 10 mg I.M. approximately 30 minutes prior to procedure. As preoperative medication, 10 mg I.M.; in cardioversion, 5 to 15 mg I.V. within 5 to 10 minutes prior to procedure. Once acute symptomatology has been properly controlled with injectable form, patient may be placed on oral form if further treatment is required.

Management of Overdosage: Manifestations include somnolence, confusion, coma, diminished reflexes. Monitor respiration, pulse, blood pressure; employ general supportive measures, I.V. fluids, adequate airway. Hypotension may be combated by the use of levarterenol or metaraminol. Dialysis is of limited value.

Supplied: Ampuls, 2 ml, boxes of 10; Vials, 10 ml, boxes of 1; Tel-E-Ject® (disposable syringes), 2 ml, boxes of 10. Each ml contains 5 mg diazepam compounded with 40% propylene glycol, 10% ethyl alcohol, 5% sodium benzoate and benzoic acid as buffers, and 1.5% benzyl alcohol as preservative.

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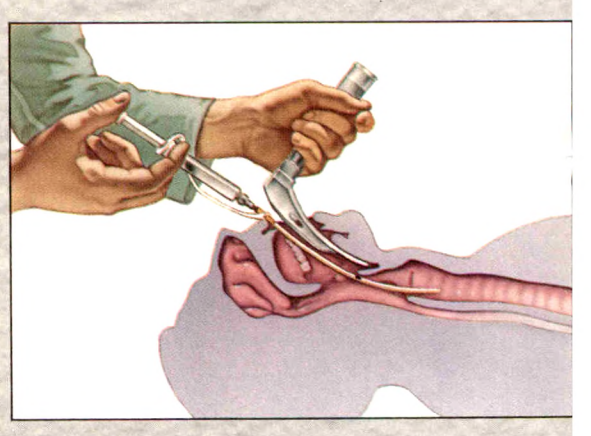
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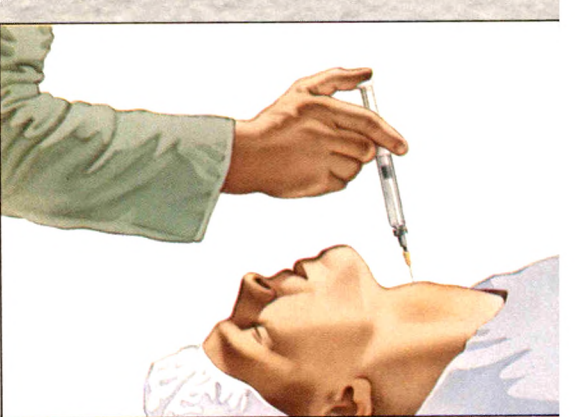
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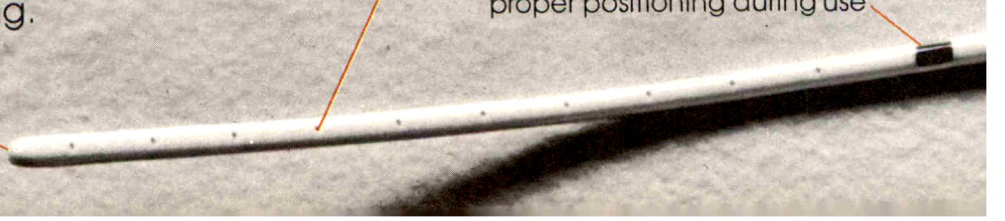
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- upward spray ensures 360° coverage
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25% more drug than other kits*

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- lets you choose either intraoral or transtracheal routes of administration at your discretion

Cannula

- anatomically curved to facilitate introduction into larynx and trachea.
- easily attaches to syringe, virtually no assembly time

*Although absorption of lidocaine from respiratory mucosa varies widely among individuals, blood concentrations achieved by this route can rise to levels comparable to those reached by similar doses infused intravenously, and in some cases almost as rapidly.[1,2,3]

REFERENCES

1. Bromage P: Concentrations of lidocaine in the blood after intravenous and endotracheal administration. *Anaesthesia*, 16:461, 1961.
2. Chu S: Plasma concentration of lidocaine after endotracheal spray. *Anesth. Analg.*, 54:438, 1975.
3. Pelton D: Plasma lidocaine concentrations following topical aerosol application to the trachea and bronchi. *Canad. Anaesth. Soc. J.*, 17:250, 1970.

ASTRA®

Astra Pharmaceutical Products, Inc.
Worcester, Massachusetts 01606

(Please see following page for a brief summary of prescribing information.)

Xylocaine®
(lidocaine hydrochloride)
4% Sterile Solution

Before prescribing or administering, please consult complete product information, a summary of which follows:

CONTRAINDICATIONS: Lidocaine hydrochloride sterile solution is contraindicated in patients with a known history of hypersensitivity either to local anesthetics of the amide type or to other components of the sterile solution.

PRECAUTIONS: The safety and effectiveness of lidocaine hydrochloride depend on proper dosage, correct technique, adequate precautions, and readiness for emergencies. Standard textbooks should be consulted for specific techniques and precautions for various anesthetic procedures.

The lowest dosage that results in effective anesthesia should be used. Injection of repeated doses of lidocaine hydrochloride may cause significant increases in blood levels with each repeated dose due to slow accumulation of the drug or its metabolites. Tolerance varies with the status of the patient. Debilitated, elderly patients, acutely ill patients, and children should be given reduced doses commensurate with their age and physical status. Lidocaine hydrochloride should also be used with caution in patients with severe shock or heart block.

As with all injections of local anesthetics, retrobulbar injection should always be made slowly and with frequent aspirations.

Solutions to which a vasoconstrictor has been added should be used with caution in the presence of diseases which may adversely affect the patient's cardiovascular system. Serious cardiac arrhythmias may occur if preparations containing a vasoconstrictor are employed in patients during or following the administration of chloroform, halothane, cyclopropane, trichlorethylene, or other related agents.

Lidocaine hydrochloride should be used with caution in persons with known drug sensitivities. Patients allergic to para-aminobenzoic acid derivatives (procaine, tetracaine, benzocaine, etc.) have not shown cross sensitivity to lidocaine HCl.

Local anesthetics react with certain metals and cause the release of their respective ions which, if injected, may cause severe local irritation. Adequate precaution should be taken to avoid this type of interaction.

The safety of amide local anesthetics in patients with malignant hyperthermia has not been assessed, and therefore, those agents should be used with caution in such patients.

Drowsiness following lidocaine hydrochloride injection is *usually* an early indication of a high blood level of the drug and may occur following inadvertent intravascular administration or *rapid absorption* of lidocaine.

ADVERSE REACTIONS: Adverse reactions may result from high plasma levels due to excessive dosage, rapid absorption or inadvertent intravascular injection. Such reactions are systemic in nature and involve the central nervous system and/or the cardiovascular system. A small number of reactions may result from hypersensitivity, idiosyncrasy or diminished tolerance on the part of the patient.

CNS reactions are excitatory and/or depressant, and may be characterized by nervousness, dizziness, blurred vision and tremors, followed by drowsiness, convulsions, unconsciousness and possibly respiratory arrest. The excitatory reactions may be very brief or may not occur at all, in which case the first manifestations of toxicity may be drowsiness, merging into unconsciousness and respiratory arrest.

Toxic cardiovascular reactions to local anesthetics are usually depressant in nature and are characterized by hypotension, myocardial depression, bradycardia and possibly cardiac arrest.

Treatment of a patient with toxic manifestations consists of assuring and maintaining a patent airway, supporting ventilation with oxygen, and assisted or controlled ventilation (respiration) as required. This usually will be sufficient in the management of most reactions. Should a convulsion persist despite ventilation therapy, small increments of anticonvulsive agents may be given intravenously. Examples of such agents include benzodiazepine (e.g., diazepam), ultrashort acting barbiturates (e.g., thiopental or thiamylal) or a short acting barbiturate (e.g., pentobarbital or secobarbital). Cardiovascular depression may require circulatory assistance with intravenous fluids and/or vasopressors (e.g., ephedrine) as dictated by the clinical situation.

Allergic reactions may occur as a result of sensitivity either to local anesthetics or to other components of the sterile solution. Anaphylactoid type symptomatology and reactions, characterized by cutaneous lesions, urticaria, edema, should be managed by conventional means. The detection of potential sensitivity by skin testing is of limited value.

HOW SUPPLIED: Xylocaine (lidocaine hydrochloride) 4% Sterile Solution:
5 ml ampule, package of 10; 5 ml prefilled sterile disposable syringe.

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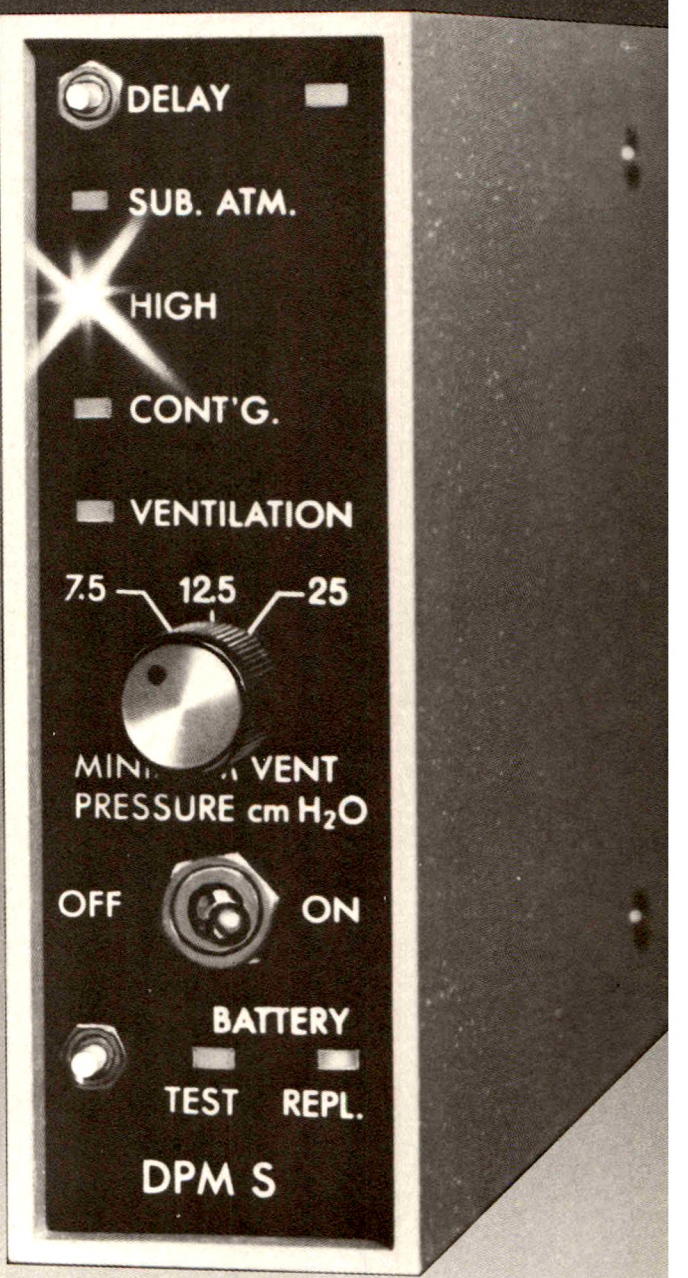
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Antiemetic activity	**Signifi-cant**	No	No	Mild
Alpha-adrenergic blockade	**YES**	No	No	No
May be used both IM and IV	**YES**	Yes (IM preferred)	Yes	No
Less pain on injection	**YES**	No	No	No
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Please see brief summary of Prescribing Information on next page.

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DESCRIPTION:
2 ml. and 5 ml. ampoules
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Droperidol . . . . . 2.5 mg.
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Droperidol is a neuroleptic (tranquilizer) agent.

INDICATIONS: INAPSINE (droperidol) is indicated:
to produce tranquilization and to reduce the incidence of nausea and vomiting in surgical and diagnostic procedures;
for premedication, induction, and as an adjunct in the maintenance of general and regional anesthesia;
in neuroleptanalgesia in which INAPSINE (droperidol) is given concurrently with a narcotic analgesic, such as SUBLIMAZE® (fentanyl) injection, to aid in producing tranquility and decreasing anxiety and pain.

CONTRAINDICATIONS: INAPSINE (droperidol) is contraindicated in patients with known intolerance to the drug.

WARNINGS: FLUIDS AND OTHER COUNTERMEASURES TO MANAGE HYPOTENSION SHOULD BE READILY AVAILABLE. As with other CNS depressant drugs, patients who have received INAPSINE (droperidol) should have appropriate surveillance.
If INAPSINE (droperidol) is administered with a narcotic analgesic such as SUBLIMAZE (fentanyl), the user should familiarize himself with the special properties of each drug, particularly the widely differing durations of action. In addition, when such a combination is used, resuscitative equipment and a narcotic antagonist should be readily available to manage apnea. See package insert for fentanyl before using. Narcotic analgesics such as SUBLIMAZE (fentanyl) may cause muscle rigidity, particularly involving the muscles of respiration. This effect is related to the speed of injection. Its incidence can be reduced by the use of slow intravenous injection. Once this effect occurs, it is managed by the use of assisted or controlled respiration and, if necessary, by a neuromuscular blocking agent compatible with the patient's condition.
The respiratory depressant effect of narcotics persists longer than their measured analgesic effect. When used with INAPSINE (droperidol), the total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, be used initially in reduced doses as low as ¼ to ⅓ those usually recommended.

PRECAUTIONS: The initial dose of INAPSINE (droperidol) should be appropriately reduced in elderly, debilitated and other poor-risk patients. The effect of the initial dose should be considered in determining incremental doses. Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can cause peripheral vasodilatation and hypotension because of sympathetic blockade. Through other mechanisms INAPSINE (droperidol) can also alter circulation. Therefore, when INAPSINE (droperidol) is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for this form of anesthesia.
If hypotension occurs, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should also be considered when operative conditions permit. It should be noted that in spinal and peridural anesthesia, tilting the patient into a head down position may result in a higher level of anesthesia than is desirable, as well as impair venous return to the heart. Care should be exercised in moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do not correct the hypotension, then the administration of pressor agents other than epinephrine should be considered. Epinephrine may paradoxically decrease the blood pressure in patients treated with INAPSINE (droperidol) due to the alpha-adrenergic blocking action of droperidol.
Since INAPSINE (droperidol) may decrease pulmonary arterial pressure, this fact should be considered by those who conduct diagnostic or surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient. Vital signs should be monitored routinely.
Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, and general anesthetics) have additive or potentiating effects with INAPSINE (droperidol). When patients have received such drugs, the dose of INAPSINE (droperidol) required will be less than usual. Likewise, following the administration of INAPSINE (droperidol), the dose of other CNS depressant drugs should be reduced.
INAPSINE (droperidol) should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.
When the EEG is used for postoperative monitoring, it may be found that the EEG pattern returns to normal slowly.
Since INAPSINE (droperidol) is frequently used with the narcotic analgesic SUBLIMAZE (fentanyl), it should be noted that fentanyl may produce bradycardia, which may be treated with atropine; however, fentanyl should be used with caution in patients with cardiac bradyarrhythmias.*

ADVERSE REACTIONS: The most common adverse reactions reported to occur with INAPSINE (droperidol) are mild to moderate hypotension and occasionally tachycardia, but these effects usually subside without treatment. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Postoperative drowsiness is also frequently reported.
Extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed following administration of INAPSINE (droperidol). Restlessness, hyperactivity, and anxiety which can be either the result of inadequate dosage of INAPSINE (droperidol) or a part of the symptom complex of akathisia may occur. When extrapyramidal symptoms occur, they can usually be controlled with anti-parkinson agents.
Other adverse reactions that have been reported are dizziness, chills and/or shivering, laryngospasm, bronchospasm and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression).
When INAPSINE (droperidol) is used with a narcotic analgesic such as SUBLIMAZE (fentanyl), respiratory depression, apnea, and muscular rigidity can occur; if these remain untreated respiratory arrest could occur. Elevated blood pressure, with or without preexisting hypertension, has been reported following administration of INAPSINE (droperidol) combined with SUBLIMAZE (fentanyl) or other parenteral analgesics. This might be due to unexplained alterations in sympathetic activity following large doses; however, it is also frequently attributed to anesthetic or surgical stimulation during light anesthesia.

DOSAGE AND ADMINISTRATION: Dosage should be individualized. Some of the factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and the surgical procedure involved. Vital signs should be monitored routinely.
Usual Adult Dosage

I. Premedication—(to be appropriately modified in the elderly, debilitated, and those who have received other depressant drugs) 2.5 to 10 mg. (1 to 4 ml.) may be administered intramuscularly 30 to 60 minutes preoperatively.

II. Adjunct to General Anesthesia
Induction—2.5 mg. (1 ml.) per 20 to 25 pounds may be administered (usually intravenously) along with an analgesic and/or general anesthetic. Smaller doses may be adequate. The total amount of INAPSINE (droperidol) administered should be titrated to obtain the desired effect based on the individual patient's response.
Maintenance—1.25 to 2.5 mg. (0.5 to 1 ml.) usually intravenously (see warning regarding use with concomitant narcotic analgesic medication and the possibility of widely differing durations of action).
If INNOVAR® injection is administered in addition to INAPSINE (droperidol), the calculation of the recommended dose of INAPSINE (droperidol) should include the droperidol contained in the INNOVAR injection. See INNOVAR injection Package Insert for full prescribing information.

III. Use Without A General Anesthetic In Diagnostic Procedures—Administer the usual I.M. premedication 2.5 to 10 mg. (1 to 4 ml.) 30 to 60 minutes before the procedure. Additional 1.25 to 2.5 mg. (0.5 to 1 ml.) amounts of INAPSINE (droperidol) may be administered, usually intravenously (see warning regarding use with concomitant narcotic analgesic medication and the possibility of widely differing durations of action).
Note: When INAPSINE (droperidol) is used in certain procedures, such as bronchoscopy, appropriate topical anesthesia is still necessary.

IV. Adjunct to Regional Anesthesia—2.5 to 5 mg. (1 to 2 ml.) may be administered intramuscularly or slowly intravenously when additional sedation is required.

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25 mg in a 5 ml vial
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References: **1.** Gyermek L: *Curr Ther Res* 18:377-386, 1975. **2.** Katz RL: *Anesthesiology* 28:528-534, 1967.

BRIEF SUMMARY—(Please consult full package insert, enclosed in every package, before using Regonol)

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When used as an antagonist to nondepolarizing muscle relaxants, adequate recovery of voluntary respiration and neuromuscular transmission must be obtained prior to discontinuation of respiratory assistance and there should be continuous patient observation. Satisfactory recovery may be defined by a combination of clinical judgement, respiratory measurements and observation of the effects of peripheral nerve stimulation. If there is any doubt concerning the adequacy of recovery from the effects of the nondepolarizing muscle relaxant, artificial ventilation should be continued until all doubt has been removed.

Use in Pregnancy—The safety of pyridostigmine bromide during pregnancy or lactation in humans has not been established. Therefore its use in women who are pregnant requires weighing the drug's potential benefits against its possible hazards to mother and child.

ADVERSE REACTIONS—The side effects of pyridostigmine bromide are most commonly related to overdosage and generally are of two varieties, muscarinic and nicotinic. Among those in the former group are nausea, vomiting, diarrhea, abdominal cramps, increased peristalsis, increased salivation, increased bronchial secretions, miosis and diaphoresis. Nicotinic side effects are comprised chiefly of muscle cramps, fasciculation and weakness. Muscarinic side effects can usually be counteracted by atropine. As with any compound containing the bromide radical, a skin rash may be seen in an occasional patient. Such reactions usually subside promptly upon discontinuance of the medication. Thrombophlebitis has been reported subsequent to intravenous administration.

DOSAGE AND ADMINISTRATION—When pyridostigmine bromide is given intravenously to reverse the action of muscle relaxant drugs, it is recommended that atropine sulfate (0.6 to 1.2 mg.) or glycopyrrolate in equipotent doses be given intravenously immediately prior to or simultaneous with its administration. Side effects, notably excessive secretions and bradycardia are thereby minimized. Reversal dosages range from 0.1-0.25 mg./kg. Usually 10 or 20 mg. of pyridostigmine bromide will be sufficient for antagonism of the effects of the nondepolarizing muscle relaxants. Although full recovery may occur within 15 minutes in most patients, others may require a half hour or more. Satisfactory reversal can be evident by adequate voluntary respiration, respiratory measurements and use of a peripheral nerve stimulator device. It is recommended that the patient be well ventilated and a patent airway maintained until complete recovery of normal respiration is assured. Once satisfactory reversal has been attained recurarization has not been reported.

Failure of pyridostigmine bromide to provide prompt (within 30 minutes) reversal may occur e.g. in the presence of extreme debilitation, carcinomatosis, or with concomitant use of certain broad spectrum antibiotics or anesthetic agents, notably ether. Under these circumstances ventilation must be supported by artificial means until the patient has resumed control of his respiration.

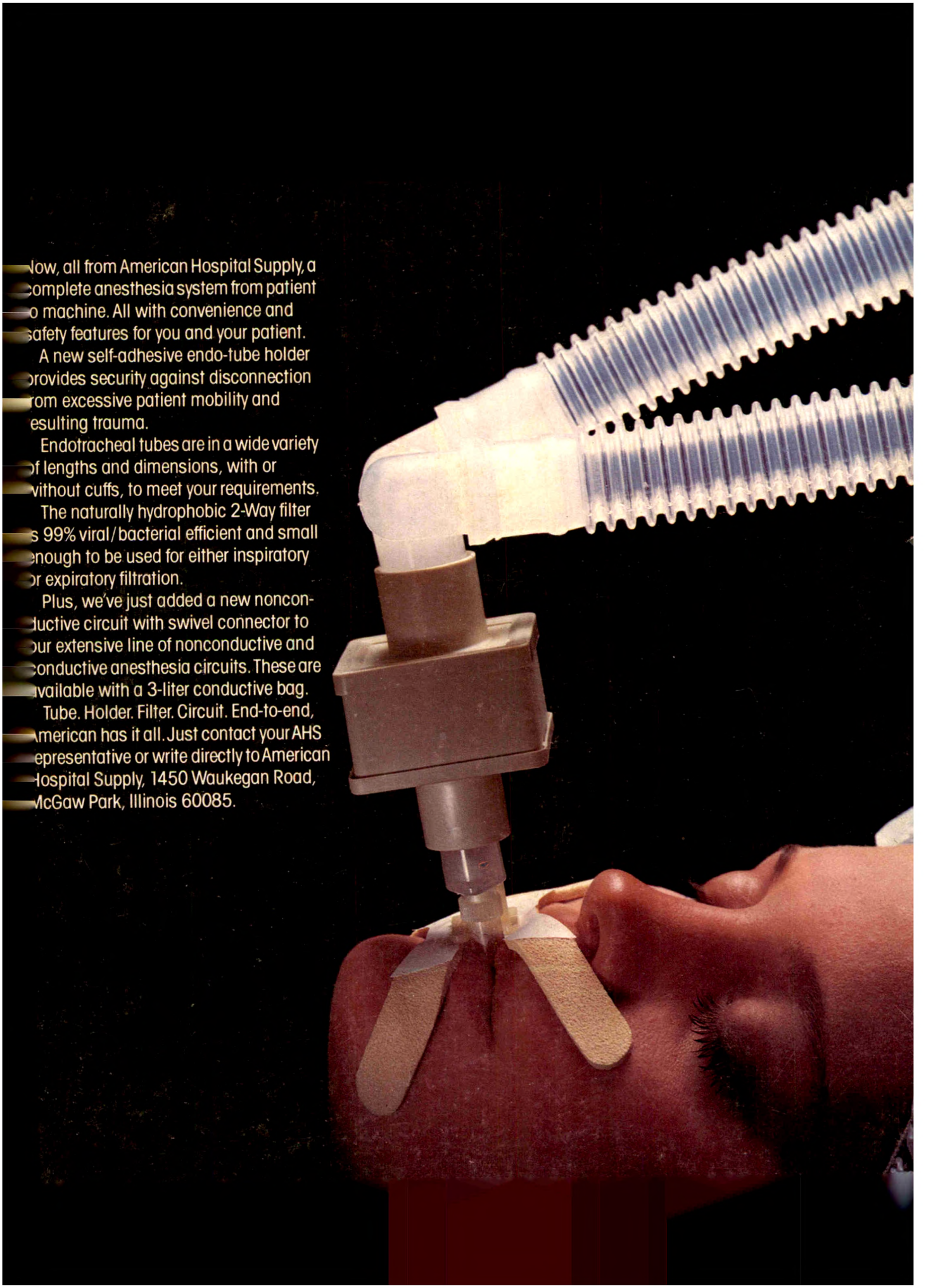
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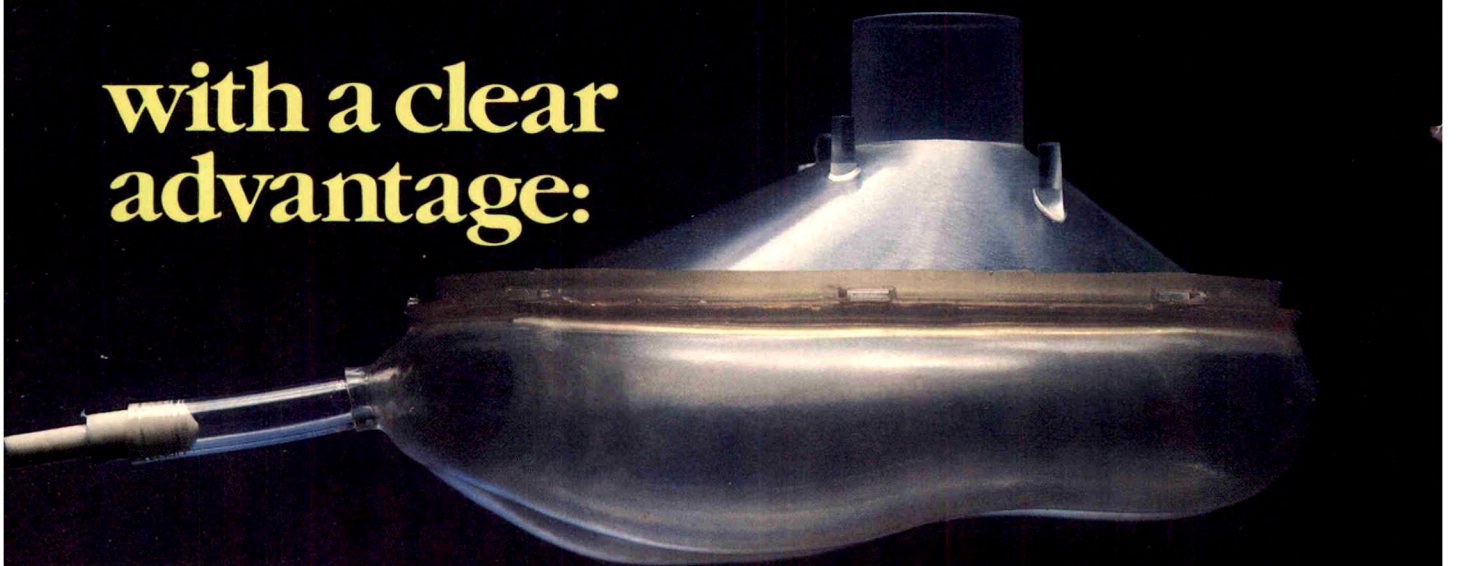
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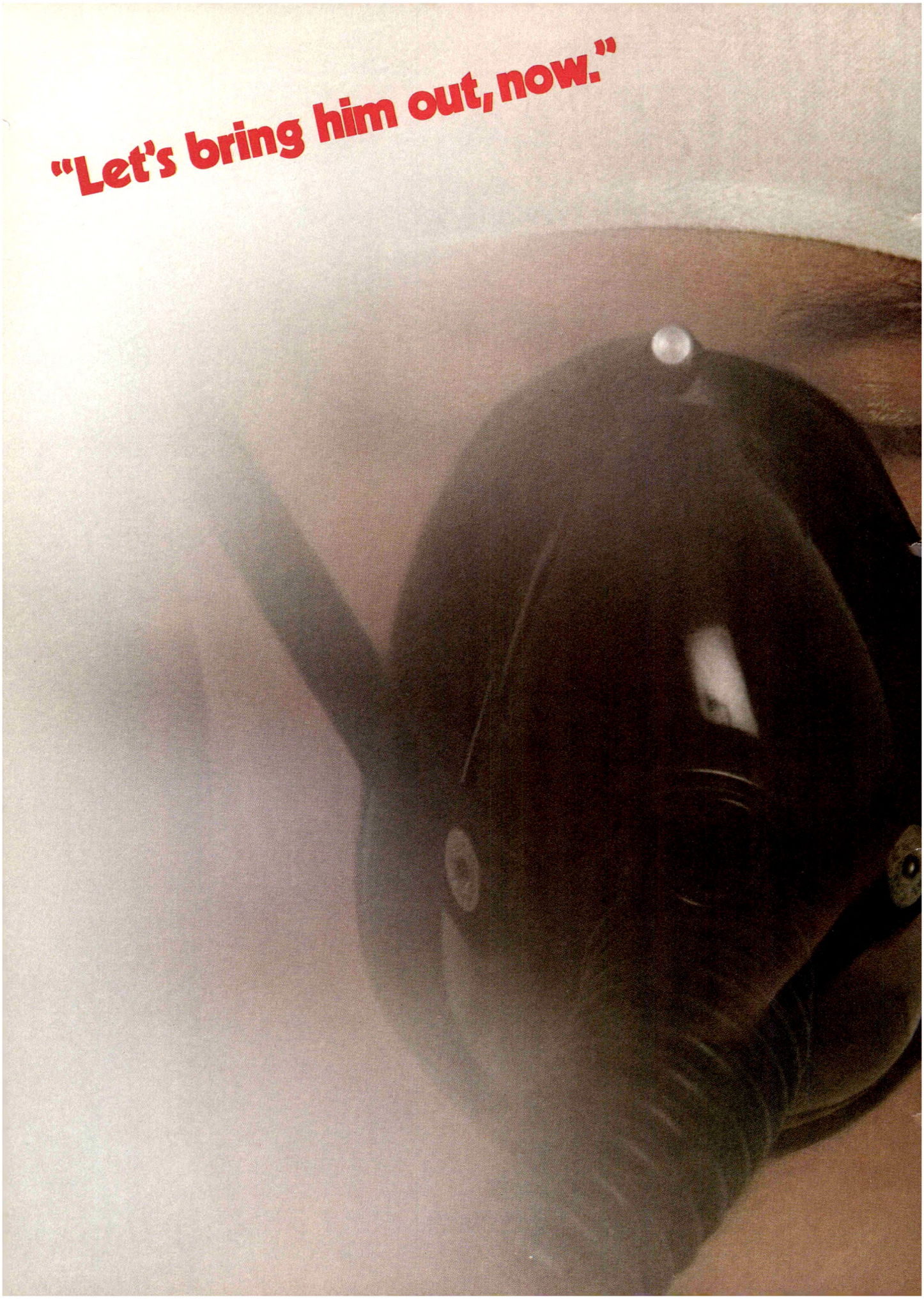
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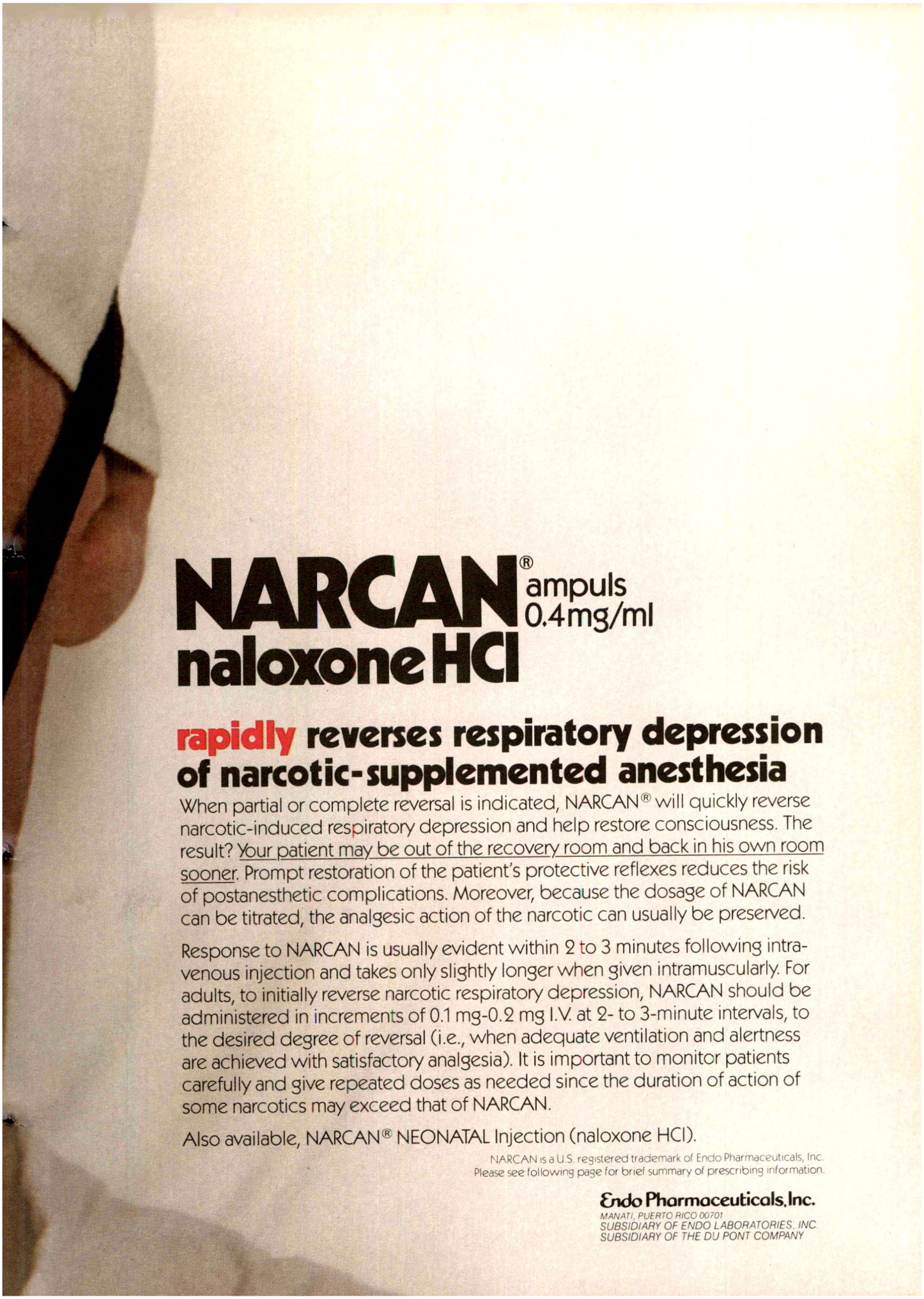
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CONTRAINDICATIONS NARCAN is contraindicated in patients known to be hypersensitive to it.

WARNINGS NARCAN should be administered cautiously to persons including newborns of mothers who are known or suspected to be physically dependent on opioids. In such cases an abrupt and complete reversal of narcotic effects may precipitate an acute abstinence syndrome.

The patient who has satisfactorily responded to NARCAN should be kept under continued surveillance and repeated doses of NARCAN should be administered, as necessary, since the duration of action of some narcotics may exceed that of NARCAN.

NARCAN is not effective against respiratory depression due to non-opioid drugs.

Usage in Pregnancy: Safe use of NARCAN during pregnancy (other than labor) has not been established. Animal reproduction studies have not demonstrated teratogenic or other embryotoxic effects (See ANIMAL PHARMACOLOGY AND TOXICOLOGY). However, NARCAN should be administered to pregnant patients only when, in the judgment of the physician, the potential benefits outweigh the possible hazards.

PRECAUTIONS In addition to NARCAN, other resuscitative measures such as maintenance of a free airway, artificial ventilation, cardiac massage, and vasopressor agents should be available and employed when necessary to counteract acute narcotic poisoning. In an isolated report two patients with preexisting ventricular irritability requiring lidocaine, and either isoproterenol or epinephrine for hypotension following cardiopulmonary bypass procedures, developed ventricular tachycardia or fibrillation when given NARCAN I.V. at 9 and 14 hours, respectively, postoperatively for persistent unresponsiveness. Although a direct cause and effect relationship has not been established, NARCAN should be used with caution in patients with cardiac irritability.

In rare cases very rapid reversal of narcotic anesthesia in cardiac patients has resulted in pulmonary edema.

ADVERSE REACTIONS Abrupt reversal of narcotic depression may result in nausea, vomiting, sweating, tachycardia, increased blood pressure, and tremulousness. In postoperative patients, excessive dosage of NARCAN may result in significant reversal of analgesia, and excitement, in some cardiac patients, the resultant hypertension and tachycardia may result in left ventricular failure and pulmonary edema. In the absence of narcotics naloxone is essentially devoid of side effects.

DOSAGE AND ADMINISTRATION NARCAN (naloxone hydrochloride) may be administered intravenously, intramuscularly, or subcutaneously. The most rapid onset of action is achieved by intravenous administration and it is recommended in emergency situations.

Since the duration of action of some narcotics may exceed that of NARCAN the patient should be kept under continued surveillance and repeated doses of NARCAN should be administered, as necessary.

USAGE IN ADULTS Narcotic Overdose—Known or Suspected The usual initial adult dose is 0.4 mg (1 ml) NARCAN administered I.V., I.M. or S.C. If the desired degree of counteraction and improvement in respiratory function is not obtained immediately following I.V. administration, it may be repeated intravenously at 2 to 3 minute intervals. Failure to obtain significant improvement after 2 or 3 doses suggests that the condition may be due partly or completely to other disease processes or non-opioid drugs.

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Repeat doses of NARCAN may be required within one to two hour intervals depending upon the amount, type (i.e. short or long acting) and time interval since last administration of narcotic. Supplemental intramuscular doses have been shown to produce a longer lasting effect.

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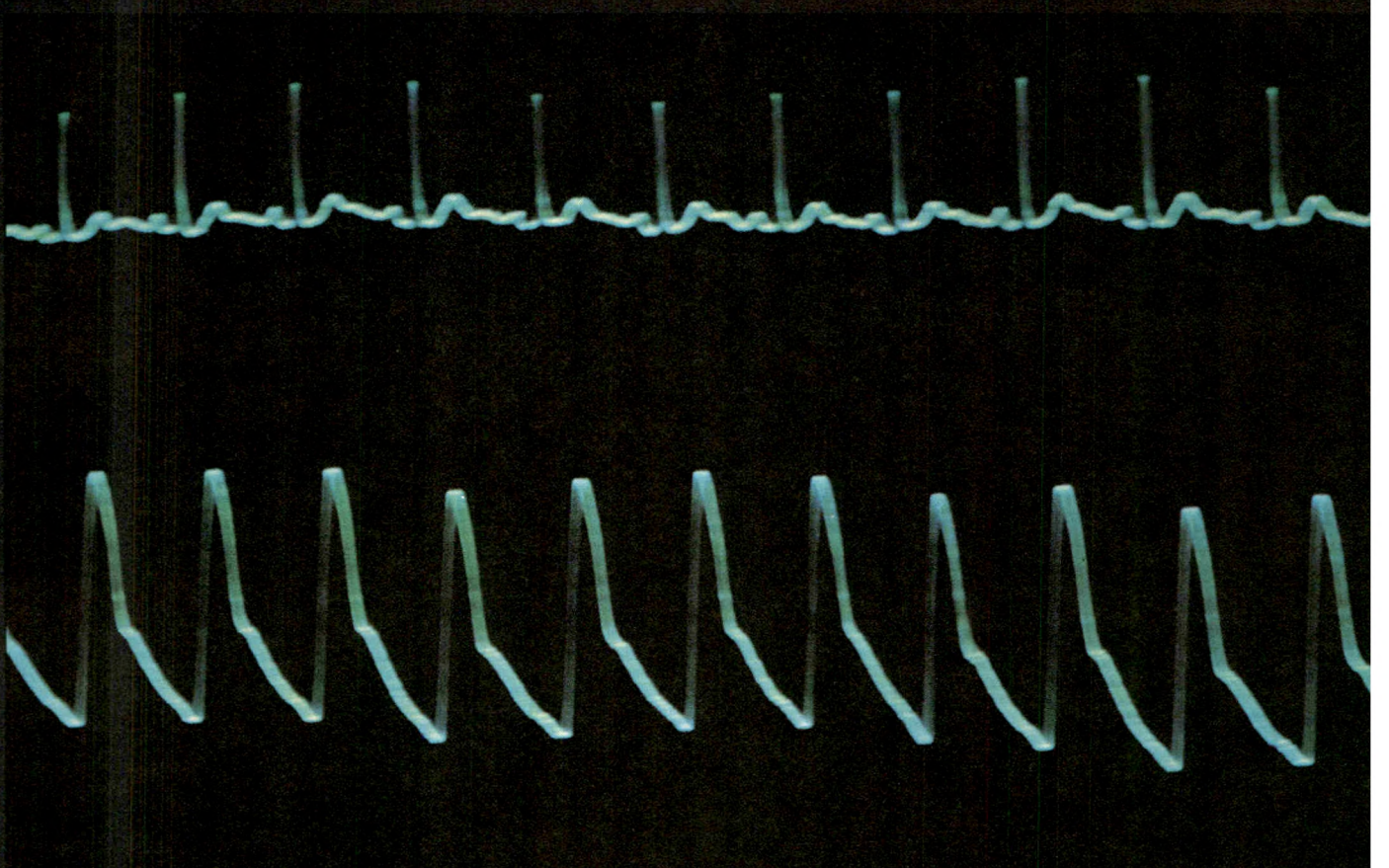
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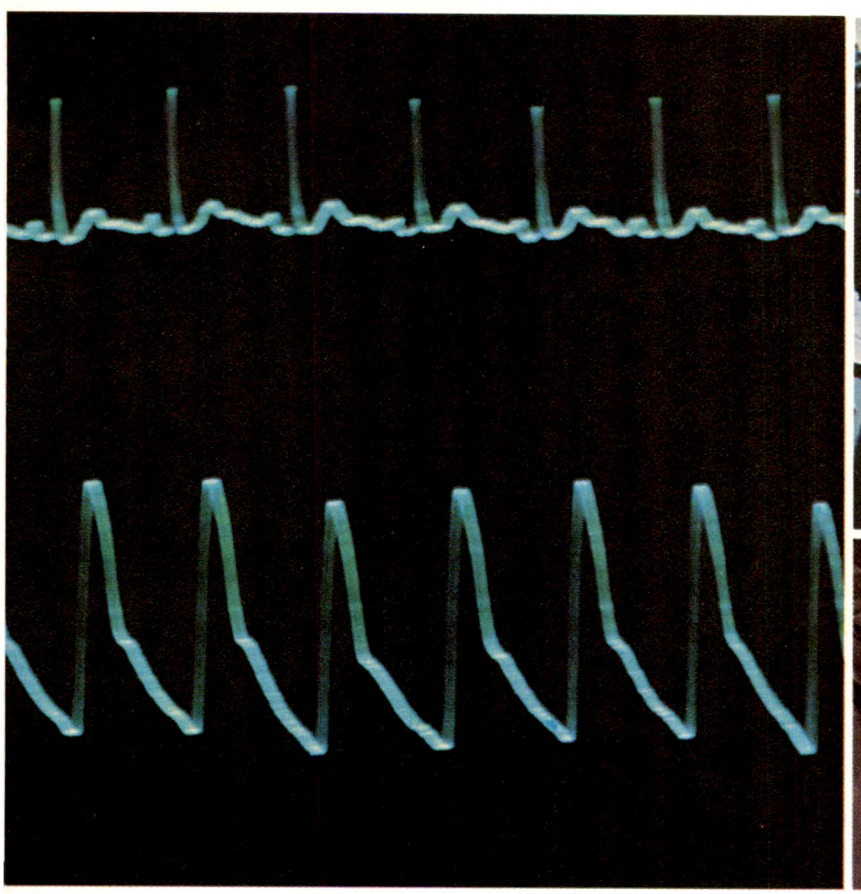
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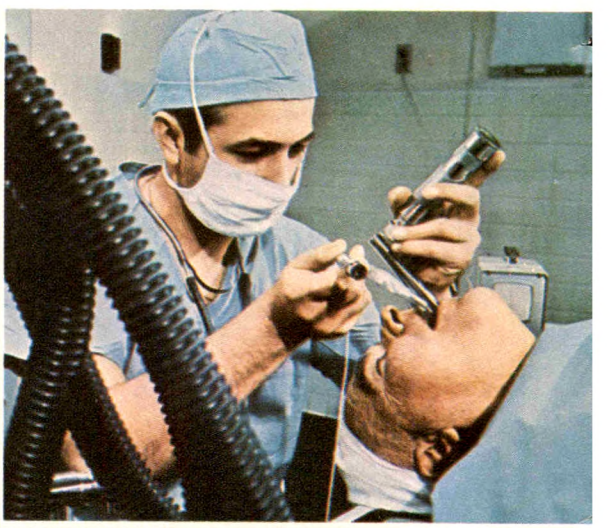


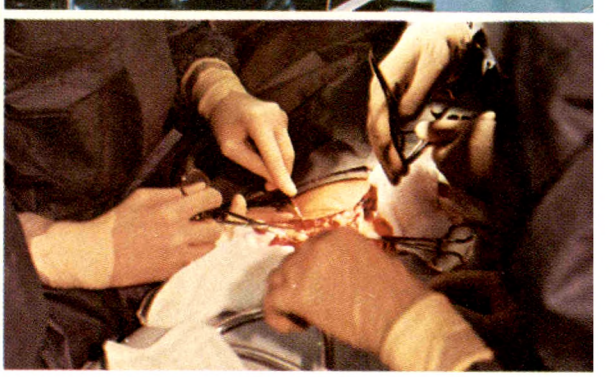
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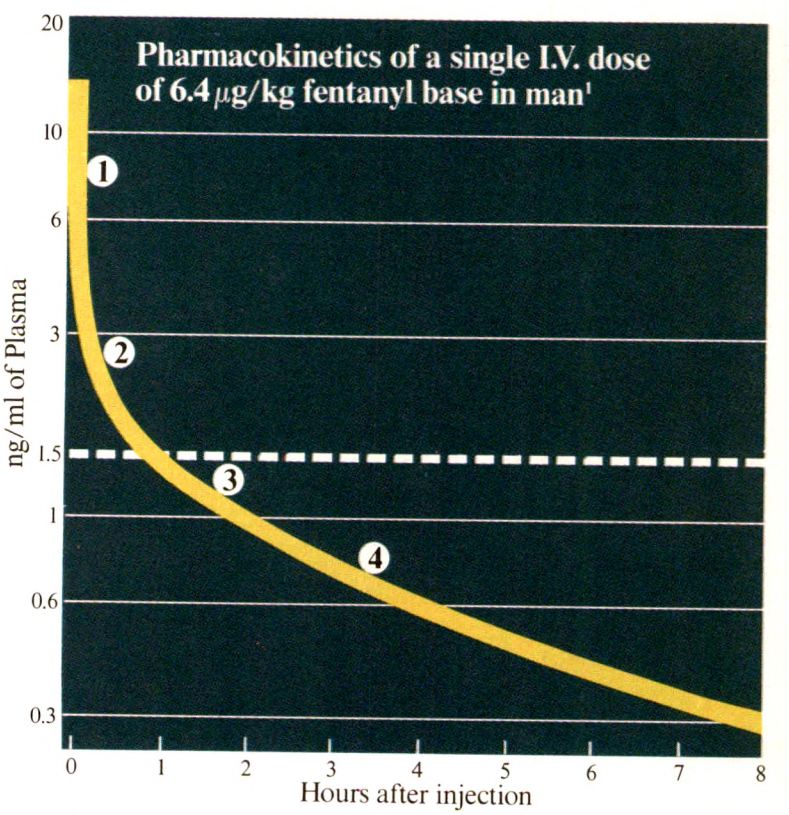
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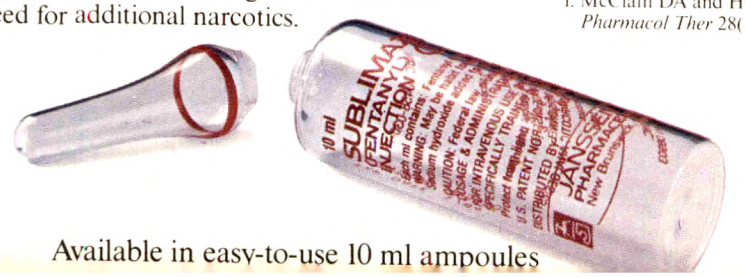
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***Note:** Respiratory depression may last longer than analgesic action and this risk increases with increasing doses.

1. McClain DA and Hug CC, Jr.: Intravenous fentanyl kinetics. *Clin Pharmacol Ther* 28(1):106-114, 1980.



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CONTRAINDICATIONS

SUBLIMAZE (fentanyl) is contraindicated in patients with known intolerance to the drug.

WARNINGS

AS WITH OTHER CNS DEPRESSANTS, PATIENTS WHO HAVE RECEIVED *SUBLIMAZE* (fentanyl) SHOULD HAVE APPROPRIATE SURVEILLANCE.

RESUSCITATION EQUIPMENT AND A NARCOTIC ANTAGONIST SHOULD BE READILY AVAILABLE TO MANAGE APNEA.

See also discussion of narcotic antagonists in Precautions and Overdosage.

If SUBLIMAZE (fentanyl) is administered with a tranquilizer such as *INAPSINE* (droperidol), the user should familiarize himself with the special properties of each drug, particularly the widely differing duration of action. In addition, when such a combination is used, *fluids and other countermeasures to manage hypotension should be available.*

As with other potent narcotics, the respiratory depressant effect of SUBLIMAZE (fentanyl) may persist longer than the measured analgesic effect. The total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, should be used in reduced doses initially, as low as ¼ to ⅓ those usually recommended. SUBLIMAZE (fentanyl) may cause muscle rigidity, particularly involving the muscles of respiration. The effect is related to the speed of injection and its incidence can be reduced by the use of slow intravenous injection. Once the effect occurs, it is managed by the use of assisted or controlled respiration and, if necessary, by a neuromuscular blocking agent compatible with the patient's condition. Where moderate or high doses are used (above 10 mcg./kg.), there must be adequate facilities for postoperative observation, and ventilation if necessary, of patients who have received SUBLIMAZE (fentanyl). It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

Drug Dependence—SUBLIMAZE (fentanyl) can produce drug dependence of the morphine type and, therefore, has the potential for being abused.

Severe and unpredictable potentiation by MAO inhibitors has been reported with narcotic analgesics. Since the safety of fentanyl in this regard has not been established, the use of SUBLIMAZE (fentanyl) in patients who have received MAO inhibitors within 14 days is not recommended.

Head Injuries and Increased Intracranial Pressure—SUBLIMAZE (fentanyl) should be used with caution in patients who may be particularly susceptible to respiratory depression, such as comatose patients who may have a head injury or brain tumor. In addition SUBLIMAZE (fentanyl) may obscure the clinical course of patients with head injury.

Usage in Children—The safety of SUBLIMAZE (fentanyl) in children younger than two years of age has not been established.

Usage in Pregnancy—The safe use of SUBLIMAZE (fentanyl) has not been established with respect to possible adverse effects upon fetal development. Therefore, it should be used in women of childbearing potential only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. There are insufficient data regarding placental transfer and fetal effects; therefore, safety for the infant in obstetrics has not been established.

PRECAUTIONS

The initial dose of SUBLIMAZE (fentanyl) should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining incremental doses. Nitrous oxide has been reported to produce cardiovascular depression when given with higher doses of fentanyl.

Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can alter respiration by blocking intercostal nerves. Through other mechanisms SUBLIMAZE (fentanyl) can also alter respiration. Therefore, when SUBLIMAZE (fentanyl) is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for these forms of anesthesia.

When used with a tranquilizer such as *INAPSINE* (droperidol), blood pressure may be altered and hypotension can occur.

Vital signs should be monitored routinely.

SUBLIMAZE (fentanyl) should be used with caution in patients with chronic obstructive pulmonary disease, patients with decreased respiratory reserve, and others with potentially compromised respiration. In such patients, narcotics may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Respiratory depression caused by narcotic analgesics can be reversed by narcotic antagonists. Appropriate surveillance should be maintained because the duration of respiratory depression of doses of fentanyl employed during anesthesia may be longer than the duration of the narcotic antagonist action. Consult individual prescribing information (levallorphan, nalorphine and naloxone) before employing narcotic antagonists.

When a tranquilizer such as *INAPSINE* (droperidol) is used with SUBLIMAZE (fentanyl) pulmonary arterial pressure may be decreased. This fact should be considered by those who conduct diagnostic and surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient. When high dose or anesthetic dosages of SUBLIMAZE (fentanyl) are employed, even relatively small dosages of diazepam may cause cardiovascular depression.

Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, and general anesthetics) will have additive or potentiating effects with SUBLIMAZE (fentanyl). When patients have received such drugs, the dose of SUBLIMAZE (fentanyl) required will be less than usual. Likewise, following the administration of SUBLIMAZE (fentanyl), the dose of other CNS depressant drugs should be reduced.

SUBLIMAZE (fentanyl) should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.

SUBLIMAZE (fentanyl) may produce bradycardia, which may be treated with atropine; however, SUBLIMAZE (fentanyl) should be used with caution in patients with cardiac bradyarrhythmias.

When SUBLIMAZE (fentanyl) is used with a tranquilizer such as *INAPSINE* (droperidol) hypotension can occur. If this occurs, the possibility of hypovolemia should also be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should be considered when operative conditions permit. Care should be exercised in moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do not correct hypotension, the administration of pressor agents other than epinephrine should be considered. Because of the alpha-adrenergic blocking action of *INAPSINE* (droperidol), epinephrine may paradoxically decrease the blood pressure in patients treated with *INAPSINE* (droperidol).

When *INAPSINE* (droperidol) is used with SUBLIMAZE (fentanyl) and the EEG is used for postoperative monitoring, it may be found that the EEG pattern returns to normal slowly.

ADVERSE REACTIONS

As with other narcotic analgesics, the most common serious adverse reactions reported to occur with SUBLIMAZE (fentanyl) are respiratory depression, apnea, muscular rigidity, and bradycardia; if these remain untreated, respiratory arrest, circulatory depression or cardiac arrest could occur. Other adverse reactions that have been reported are hypotension, dizziness, blurred vision, nausea, emesis, laryngospasm, and diaphoresis.

It has been reported that secondary rebound respiratory depression may occasionally occur postoperatively. Patients should be monitored for this possibility and appropriate countermeasures taken as necessary.

When a tranquilizer such as *INAPSINE* (droperidol) is used with SUBLIMAZE (fentanyl), the following adverse reactions can occur: chills and/or shivering, restlessness, and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression); extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed up to 24 hours postoperatively. When they occur, extrapyramidal symptoms can usually be controlled with anti-parkinson agents. Postoperative drowsiness is also frequently reported following the use of *INAPSINE* (droperidol).

Elevated blood pressure, with and without pre-existing hypertension, has been reported following administration of SUBLIMAZE (fentanyl) combined with *INAPSINE* (droperidol). This might be due to unexplained alterations in sympathetic activity following large doses; however, it is also frequently attributed to anesthetic and surgical stimulation during light anesthesia.

DOSAGE AND ADMINISTRATION

50 mcg. = .05 mg. = 1 ml.

Dosage should be individualized. Some of the factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and the surgical procedure involved.

Vital signs should be monitored routinely.

I. *Premedication*—Premedication (to be appropriately modified in the elderly, debilitated, and those who have received other depressant drugs)—50 to 100 mcg. (0.05 to 0.1 mg.)(1 to 2 ml.) may be administered *intramuscularly* 30 to 60 minutes prior to surgery.

II. *Adjunct to General Anesthesia*—See Dosage Range Chart

III. *Adjunct to Regional Anesthesia*—50 to 100 mcg. (0.05 to 0.1 mg.)(1 to 2 ml.) may be administered intramuscularly or slowly intravenously, over one to two minutes, when additional analgesia is required.

IV. *Postoperatively (recovery room)*—50 to 100 mcg. (0.05 to 0.1 mg.)(1 to 2 ml.) may be administered intramuscularly for the control of pain, tachypnea and emergence delirium. The dose may be repeated in one to two hours as needed.

Usual Children's Dosage: For induction and maintenance in children 2 to 12 years of age, a reduced dose as low as 20 to 30 mcg. (0.02 to 0.03 mg.)(0.4 to 0.6 ml.) per 20 to 25 pounds is recommended.

DOSAGE RANGE CHART

TOTAL DOSAGE

Low dose—2 mcg./kg. (.002 mg./kg.) (.04 ml./kg.) SUBLIMAZE® injection. Fentanyl in small doses is most useful for minor, but painful, surgical procedures. In addition to the analgesia during surgery, fentanyl may also provide some pain relief in the immediate postoperative period. *Maintenance:* Additional dosages of SUBLIMAZE® injection are infrequently needed in these minor procedures.

Moderate dose—2-20 mcg./kg. (.002-.02 mg./kg.)(.04-0.4 ml./kg.) SUBLIMAZE® injection. Where surgery becomes more major, a larger dose is required. With this dose, in addition to adequate analgesia, one would expect to see some abolition of the stress response. However, respiratory depression will be such that artificial ventilation during anesthesia is necessary, and careful observation of ventilation postoperatively is essential. *Maintenance:* 25 to 100 mcg. (0.025 to 0.1 mg.)(0.5 to 2.0 ml.) may be administered intravenously or intramuscularly when movement and/or changes in vital signs indicate surgical stress or lightening of analgesia.

High dose—20-50 mcg./kg. (.02-.05 mg./kg.)(0.4-1 ml./kg.) SUBLIMAZE® injection. During open heart surgery and certain more complicated neurosurgical and orthopedic procedures where surgery is more prolonged, and in the opinion of the anesthesiologist, the stress response to surgery would be detrimental to the well being of the patient, dosages of 20-50 mcg./kg. (.02-.05 mg.)(0.4-1 ml.) of SUBLIMAZE® injection with nitrous oxide oxygen have been shown to attenuate the stress response as defined by increased levels of circulating growth hormone, catecholamine, ADH, and prolactin.

When dosages in this range have been used during surgery, postoperative ventilation and observation are essential due to extended postoperative respiratory depression.

The main objective of this technique would be to produce "stress free" anesthesia. *Maintenance:* Maintenance dosage (ranging from 25 mcg. (.025 mg.)(0.5 ml.) to one half the initial loading dose) will be dictated by the changes in vital signs which indicate stress and lightening of analgesia. However, the additional dosage selected must be individualized especially if the anticipated remaining operative time is short.

As a General Anesthetic

When attenuation of the responses to surgical stress is especially important, doses of 50 to 100 mcg./kg. (.05 to 0.1 mg./kg.)(1 to 2 ml./kg.) may be administered with oxygen and a muscle relaxant. This technique has been reported to provide anesthesia without the use of additional anesthetic agents. In certain cases, doses up to 150 mcg./kg. (.15 mg./kg.)(3 ml./kg.) may be necessary to produce this anesthetic effect. It has been used for open heart surgery and certain other major surgical procedures in patients for whom protection of the myocardium from excess oxygen demand is particularly indicated, and for certain complicated neurological and orthopedic procedures.

As noted above, it is essential that qualified personnel and adequate facilities be available for the management of respiratory depression.

See Warnings and Precautions for use of SUBLIMAZE (fentanyl) with other CNS depressants, and in patients with altered response.

OVERDOSAGE

Manifestations: The manifestations of SUBLIMAZE (fentanyl) overdosage are an extension of its pharmacologic actions.

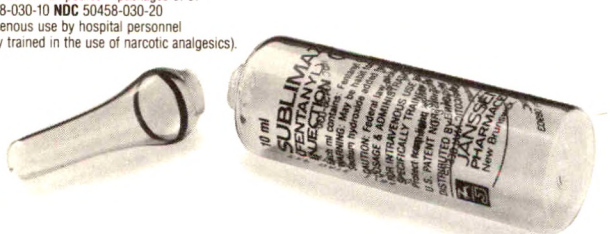
Treatment: In the presence of hypoventilation or apnea, oxygen should be administered and respiration should be assisted or controlled as indicated. A patent airway must be maintained; and oropharyngeal airway or endotracheal tube might be indicated. If depressed respiration is associated with muscular rigidity, an intravenous neuromuscular blocking agent might be required to facilitate assisted or controlled respiration. The patient should be carefully observed for 24 hours; body warmth and adequate fluid intake should be maintained. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. A specific narcotic antagonist such as nalorphine, levallorphan, or naloxone should be available for use as indicated to manage respiratory depression. This does not preclude the use of more immediate countermeasures. The duration of respiratory depression following overdosage of fentanyl may be longer than the duration of narcotic antagonist action. Consult the package insert of the individual narcotic antagonists for details about use.

HOW SUPPLIED

2 ml. and 5 ml. ampoules—packages of 10.
NDC 50458-030-02 **NDC** 50458-030-05

10 ml. and 20 ml. ampoules—packages of 5.
NDC 50458-030-10 **NDC** 50458-030-20
(For intravenous use by hospital personnel specifically trained in the use of narcotic analgesics).

March, 1980. Revised June, 1980. January, 1981
U.S. Patent No. 3, 164 600

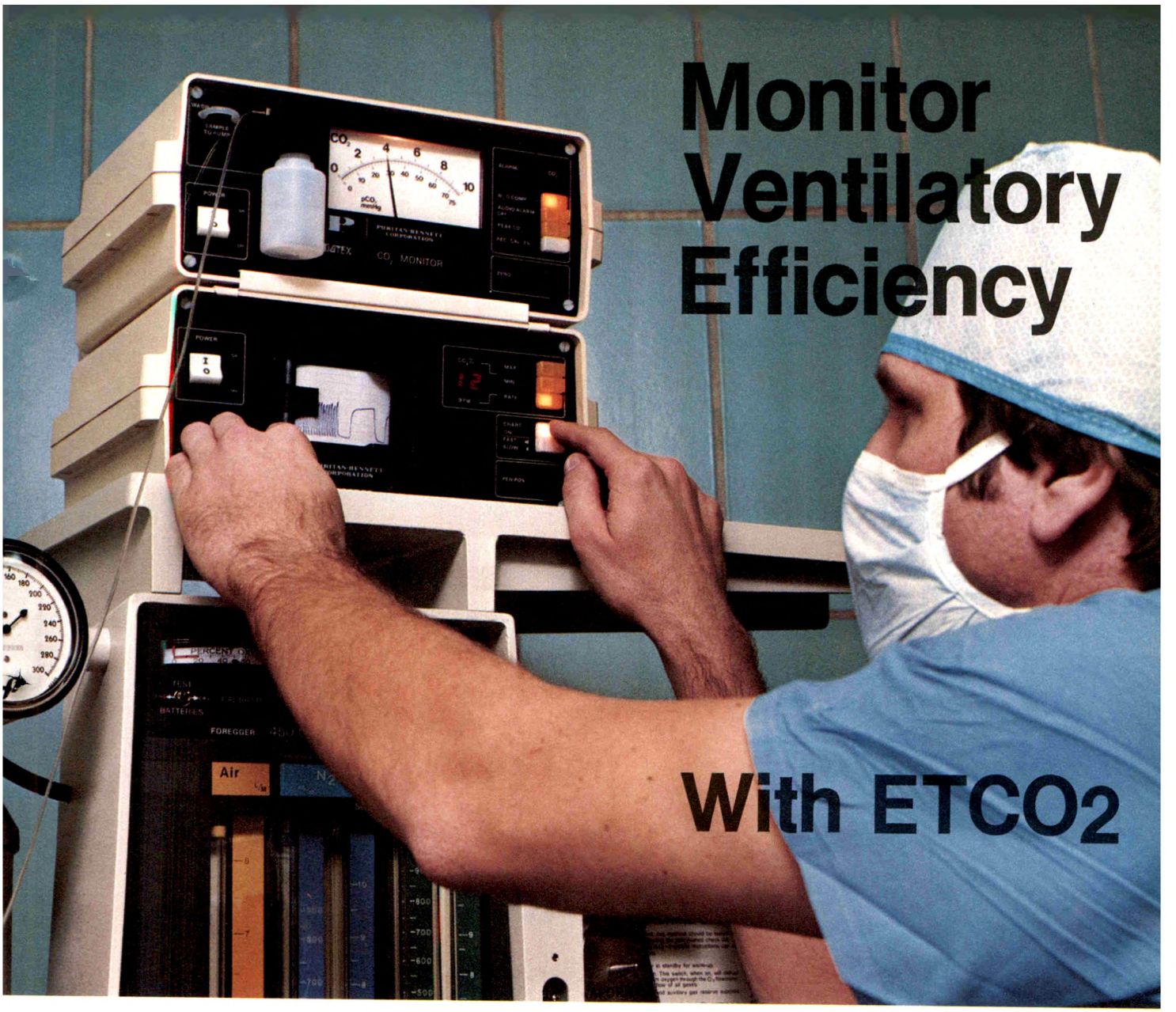


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JPI-255



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Puritan-Bennett's CO_2 Monitoring Capnography System is ideally suited for monitoring and recording your patient's respiratory CO_2 levels before, during and after surgery. The system features:

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- Simple, fast calibration
- Audible-visual CO_2 alarm
- Solid-state infrared optics
- Optional two speed strip-chart recorder with digital display of rate, minimum and maximum CO_2

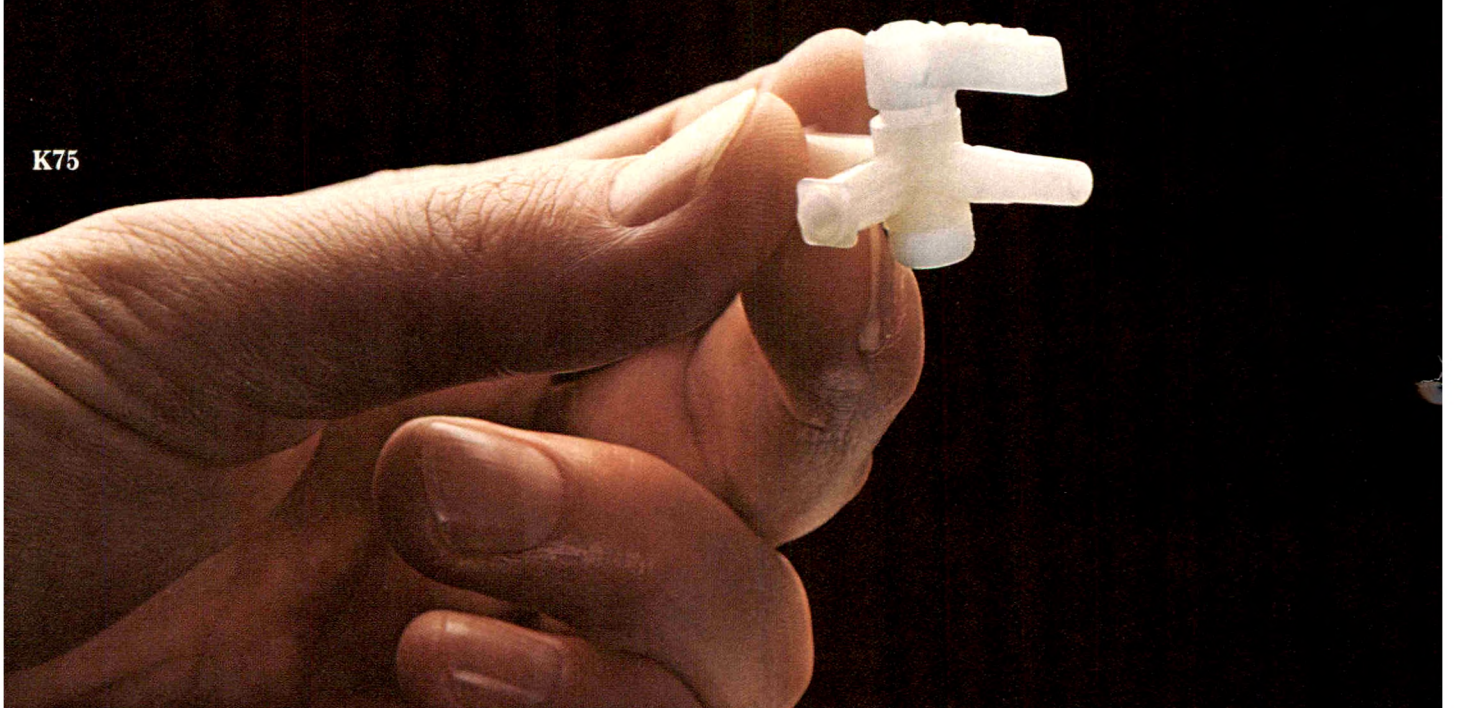
For more information on how Puritan-Bennett CO_2 Monitoring System can assist you, contact your Puritan-Bennett/Foregger Representative or Dealer.

Puritan-Bennett Corporation
Foregger Medical Division
835 Wheeler Way
Langhorne, PA 19047

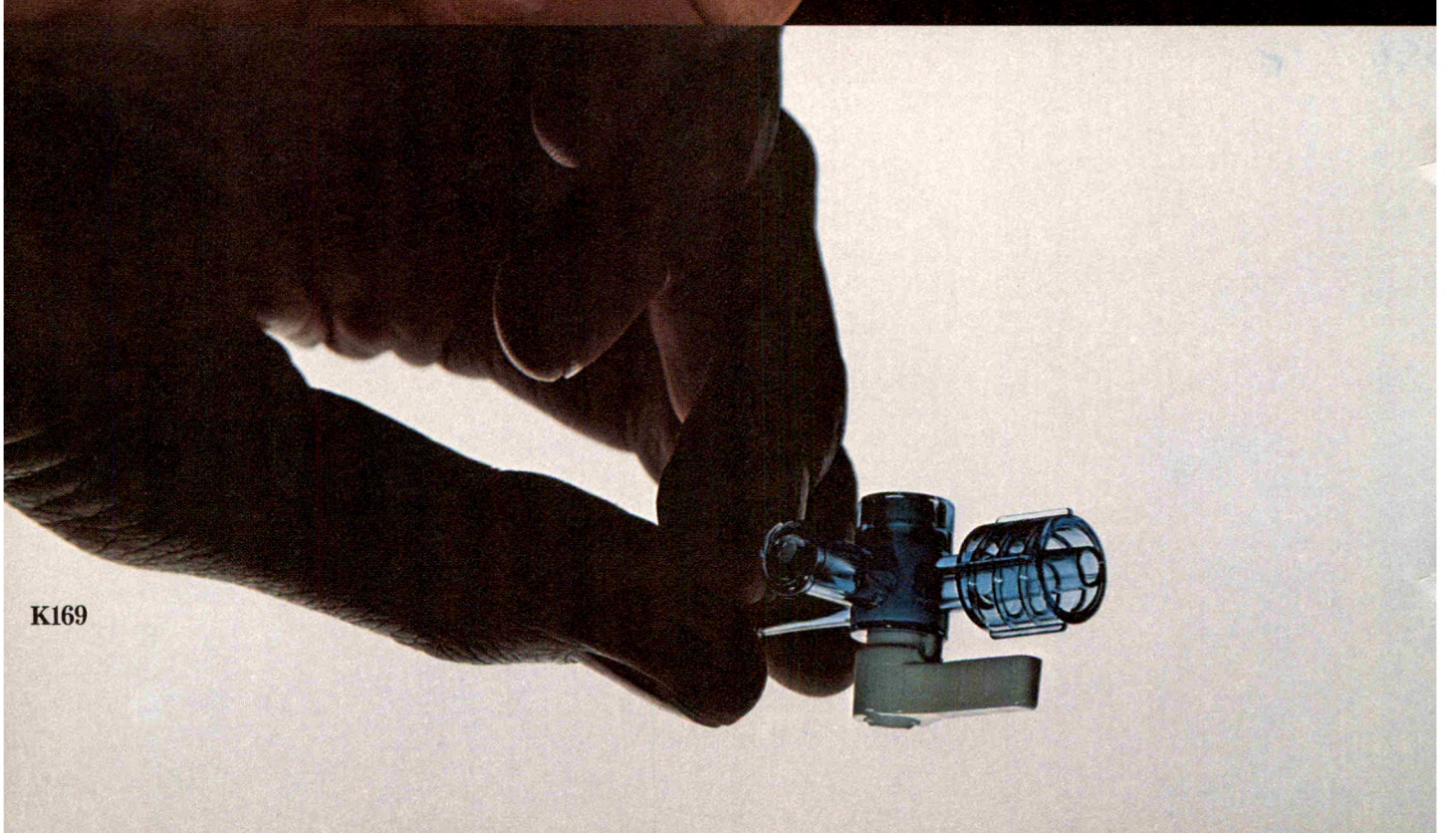
Puritan-Bennett Corporation
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Oak at Thirteenth Streets
Kansas City, MO 64106

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K75



K169

"Get me a K75..."

We're American Pharmaseal, and we make great stopcocks. In fact, you may not even know that we make them, but you sure know about them.

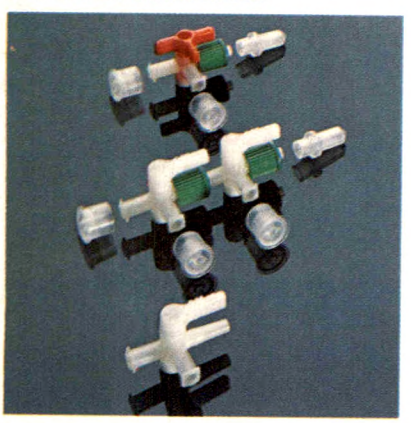
"Get me a K-75..." for example, is heard all day in hospitals all over the country.

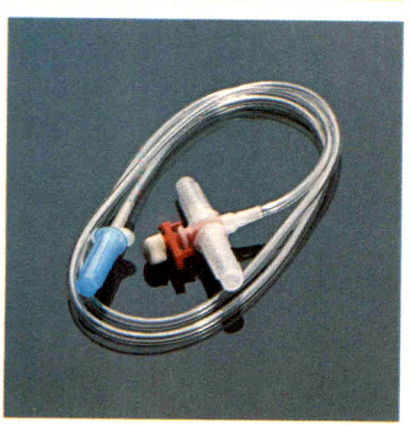
Our K-75 and K-52 Novex® stopcocks are legendary. And they're only part of the most complete and widely used line of general purpose stopcocks available anywhere.

One-way...Three-way...Double and triple tandem three-way...

The K-52 Novex with injection port.

Stopcocks with special caps to protect ports. And with rotating Luer-lock adapters for proper alignment and secure connections.





Stopcocks with a choice of pre-attached extension tubes which add up to a virtually endless variety of possible applications.

All with smooth-turning handles that won't stick or leak in the usual applications.

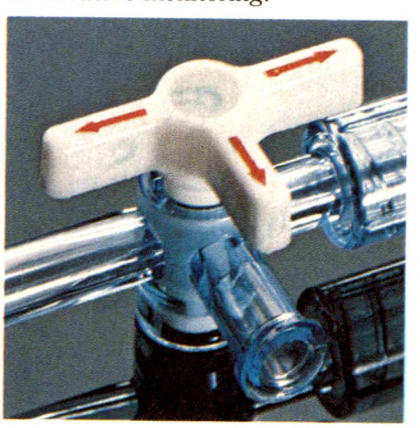
And now, a complete line of K-Series clear stopcocks for invasive monitoring.

Our latest innovation is the K-Series clear stopcocks designed for invasive monitoring.

The transparent light blue body makes air bubbles very easy to see with visual inspection. So there's no need to worry about hidden air bubbles.

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These non-leaking stopcocks feature Luer-lock fittings. They're superb units, just what you need for invasive monitoring.



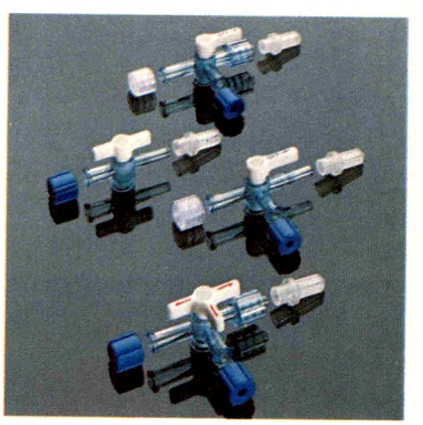
25 million later.

That's how many we've made. That's a lot of experience.

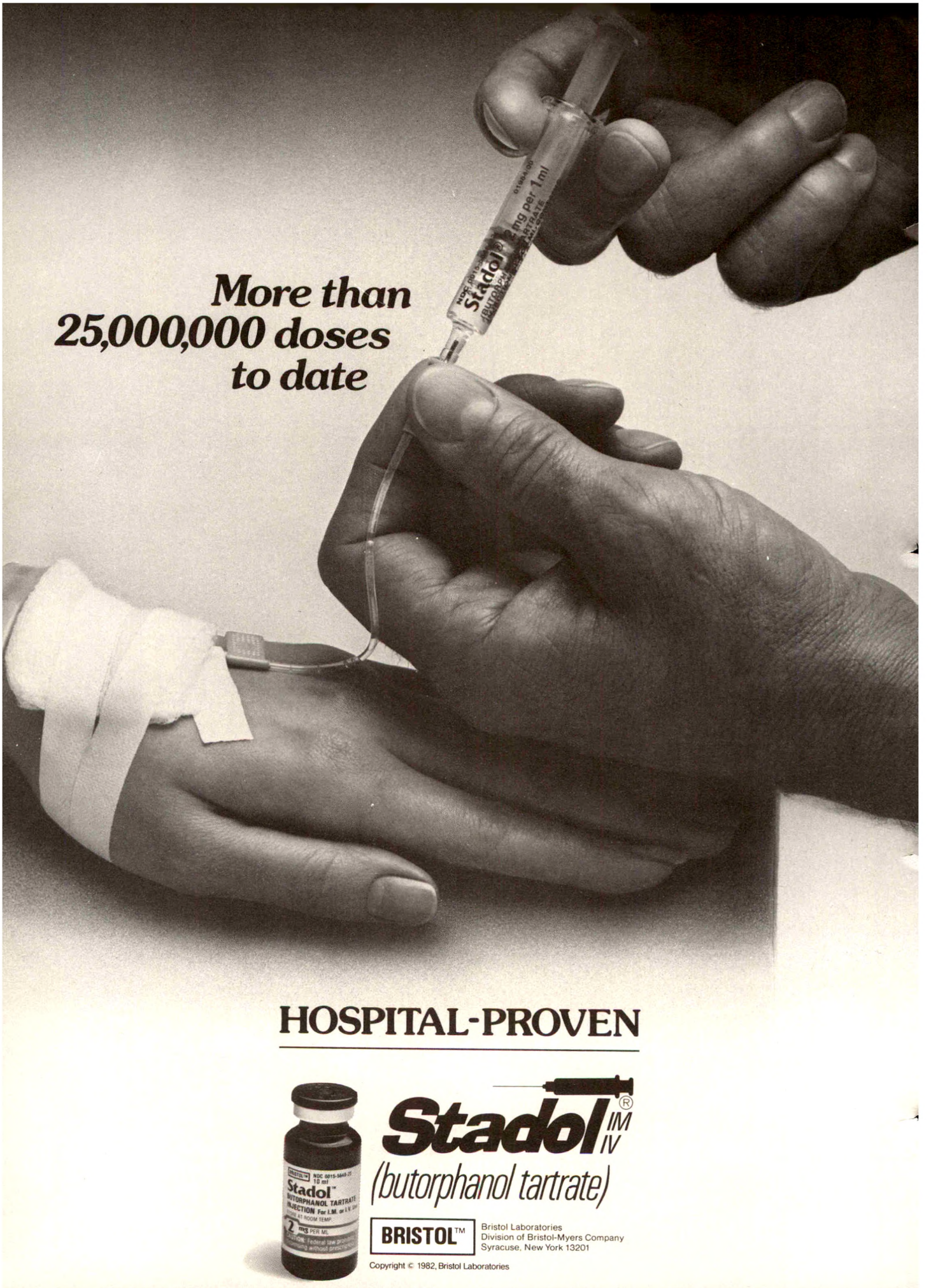
Every one is produced with the strictest quality control standards under stringent biological, chemical and physical testing.

The result, highest quality American Pharmaseal stopcocks.

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precise control . . . stability of heart rhythm . . .
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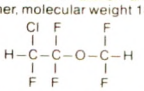
Please see complete use information on following page.

Ethrane® (enflurane)

CAUTION: Federal Law Prohibits Dispensing without Prescription.

DESCRIPTION

ETHRANE (enflurane) is a nonflammable inhalation anesthetic agent. It is 2-chloro-1, 1,2-trifluoroethyl difluoromethyl ether, molecular weight 184.5, and its structural formula is:



The boiling point is 56.5°C at 760 mm Hg, and the vapor pressure (mm Hg) is 175 at 20°C, 218 at 25°C, and 345 at 36°C. Vapor pressures can be calculated using the equation:

$\log_{10}P=A+B/T$ $A=7.967$

$B=-1678.4$

$T=°C+273.16$ (Kelvin)

The specific gravity (25°/25°C) is 1.517. The refractive index at 20° is 1.3026-1.3030. The blood/gas coefficient is 1.91 at 37°C and the oil/gas coefficient is 98.5 at 37°C. The M.A.C. (minimum alveolar concentration) in man is 1.68 percent in pure oxygen, 0.57 in 70% nitrous oxide and oxygen, and 1.17 in 30% nitrous oxide and oxygen.

ETHRANE is a clear, colorless, stable liquid whose purity exceeds 99.9 percent (area % by gas chromatography). No chemical stabilizers are added as these have been found, through controlled laboratory tests, to be unnecessary to maintain stability even in the presence of ultraviolet light. ETHRANE is stable to strong base and does not decompose in contact with soda lime and does not attack aluminum, tin, brass, iron or copper. The partition coefficients of ETHRANE at 25°C are 74 in conductive rubber and 120 in polyvinyl chloride.

CLINICAL PHARMACOLOGY

ETHRANE (enflurane) is an inhalation anesthetic. Induction and recovery from anesthesia with ETHRANE are rapid. ETHRANE has a mild, sweet odor. There is mild stimulus to salivation or tracheobronchial secretions when ETHRANE is used alone. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia changes rapidly with ETHRANE. ETHRANE reduces ventilation as depth of anesthesia increases. High pCO_2 levels can be obtained at deeper levels of anesthesia if ventilation is not supported. ETHRANE provokes a sigh response reminiscent of that seen with diethyl ether.

There is a decrease in blood pressure with induction of anesthesia, followed by a return to near normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding increases in hypotension. Heart rate remains relatively constant without significant bradycardia. Electrocardiographic monitoring or recordings indicate that cardiac rhythm remains stable. Elevation of the carbon dioxide level in arterial blood does not alter cardiac rhythm.

Studies in man indicate a considerable margin of safety in the administration of epinephrine containing solutions during ETHRANE anesthesia. ETHRANE anesthesia has been used in excision of pheochromocytoma in man without ventricular arrhythmias. On the basis of studies in patients anesthetized with ETHRANE and injected with epinephrine containing solutions to achieve hemostasis in a highly vascular area (transphenoidal surgery), it is recommended that 2 micrograms per kilogram (2μg/kg) of epinephrine may be injected subcutaneously over a 10 minute period. This may be repeated up to 3 times per hour.

Example: Up to 10 ml of 1:100,000 epinephrine containing solution (10μg/ml) may be injected subcutaneously over a 10 minute period in a 50 kilogram patient judged to have ordinary tolerance to epinephrine administration. No more than 30 ml of 1:100,000 epinephrine containing solution (10μg/ml) should be administered to such a patient per hour. The concomitant administration of lidocaine enhances the safety of the use of epinephrine during ETHRANE anesthesia. This effect of lidocaine is dose related. All customary precautions in the use of vasoconstrictor substances should be observed.

Example Two: Alternatively, up to 20 ml of 1:200,000 epinephrine containing solution (5 μg/ml) may be substituted for 10 ml of 1:100,000 solution in the above example.

Muscle relaxation may be adequate for intra-abdominal operation at normal levels of anesthesia. Muscle relaxants may be used to achieve greater relaxation and all commonly used muscle relaxants are compatible with ETHRANE. The NONDEPOLARIZING MUSCLE RELAXANTS ARE POTENTIATED. In the normal 70 kg adult, 6 to 9 mg of d-tubocurarine or 1 to 1.5 mg of pancuronium will produce a 90 percent or greater depression of twitch height. Neostigmine does not reverse the direct effect of ETHRANE.

Biotransformation of ETHRANE in man results in low levels of serum fluoride ions averaging 15 μM/L. These levels are well below the 50 μM/L threshold level which can produce minimal renal damage in normal subjects; however, it is possible that these levels could result in damage in patients with severely impaired renal function or those undergoing renal transplantation. Depression of lymphocyte transformation does not follow prolonged ETHRANE anesthesia in man in the absence of surgery. Thus ETHRANE does not depress this aspect of the immune response.

INDICATIONS

ETHRANE (enflurane) may be used for induction and maintenance of general anesthesia. Adequate data have not been developed to establish its application in obstetrical anesthesia.

CONTRAINDICATIONS

Seizure disorders (see WARNINGS).

Known sensitivity to ETHRANE (enflurane) or other halogenated anesthetics.

WARNINGS

Increasing depth of anesthesia with ETHRANE (enflurane) may produce a change in the electroencephalogram characterized by high voltage, fast frequency, progressing through spike-dome complexes alternating with periods of electrical silence to frank seizure activity. The latter may or may not be associated with motor movement. Motor activity, when encountered, generally consists of twitching or jerks of various muscle groups; it is self-limiting and can be terminated by lowering the anesthetic concentration. This electroencephalographic pattern associated with deep anesthesia is exacerbated by low arterial carbon dioxide tension. A reduction in ventilation and anesthetic concentration usually suffices to eliminate seizure activity. Cerebral blood flow and metabolism studies in normal volunteers immediately following seizure activity show no evidence of cerebral hypoxia. Mental function testing does not reveal any impairment of performance following prolonged ETHRANE anesthesia associated with or not associated with seizure activity.

Since levels of anesthesia may be altered easily and rapidly, only calibrated vaporizers which measure output with reasonable accuracy should be used. Hypotension and respiratory exchange can serve as a guide to anesthesia depth. Deep levels of anesthesia may produce marked hypotension and respiratory depression.

The action of nondepolarizing relaxants is augmented by ETHRANE. Less than the usual amounts of these drugs should be used. If the usual amounts of nondepolarizing relaxants are given, the time for recovery from myoneural blockade will be longer in the presence of ETHRANE than for other commonly used anesthetics.

Usage in Pregnancy: Safety in pregnancy has not been established. Reproduction studies have been performed in rats and rabbits, and there is no evidence of harm to the animal fetus. The relevance of these studies to the human is not known. Since there is no adequate experience in pregnant women who have received the drug, safety in pregnancy has not been established.

PRECAUTIONS

Bromsulfalein (BSP) retention is mildly elevated postoperatively in some cases. This may relate to the effect of surgery since prolonged anesthesia (5 to 7 hours) in human volunteers does not result in BSP elevation. There is some elevation of glucose and white blood count intraoperatively. Glucose elevation should be considered in diabetic patients. ETHRANE (enflurane) should be used with caution in patients who by virtue of medical or drug history could be considered more susceptible to cortical stimulation produced by this drug. As with other general anesthetics and some muscle relaxants, hyperpyrexia has been observed with the use of ETHRANE.

ADVERSE REACTIONS

1. Motor activity examplified by movements of various muscle groups and/or seizures may be encountered with deep levels of ETHRANE (enflurane) anesthesia, or light levels with hypocapnia.
2. Hypotension and respiratory depression have been reported.
3. Arrhythmias, shivering, nausea, and vomiting have been reported.
4. Elevation of the white blood count has been observed.

DOSAGE AND ADMINISTRATION

The concentration of ETHRANE (enflurane) being delivered during anesthesia from a vaporizer should be known. This may be accomplished by using:

a) vaporizers calibrated specifically for ETHRANE.

b) vaporizers from which delivered flows can easily and readily be calculated.

Nothing is present in the agent to alter calibration or affect the operation characteristics of the vaporizer.

Preanesthetic Medication: Preanesthetic medication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by ETHRANE and the heart rate remains constant: the use of anticholinergic drugs is a matter of choice.

Induction: Induction may be achieved using ETHRANE alone with oxygen or in combination with oxygen-nitrous oxide mixtures. Under these conditions some excitement may be encountered. If excitement is to be avoided, a hypnotic dose of a short-acting barbiturate should be used to induce unconsciousness, followed by the ETHRANE mixture. In general, inspired concentrations of 2.0-4.5% ETHRANE produce surgical anesthesia in 7-10 minutes.

Maintenance: Surgical levels of anesthesia may be maintained with 0.5-3% ETHRANE. Maintenance concentrations should not exceed 3%. If added relaxation is required, supplemental doses of muscle relaxants may be used. Ventilation to maintain the tension of carbon dioxide in arterial blood in the 35-45 mm Hg range is preferred. Hyperventilation should be avoided in order to minimize possible CNS excitation.

The level of blood pressure during maintenance is an inverse function of ETHRANE concentration in the absence of other complication problems. Excessive decreases (unless related to hypovolemia) may be due to depth of anesthesia and in such instances should be corrected by lightening the level of anesthesia.

Overdosage: In the event of overdosage, or what may appear to be overdosage, the following action should be taken.

Stop drug administration; establish a clear airway and initiate assisted or controlled ventilation with pure oxygen.

PACKAGING

ETHRANE (enflurane) is packaged in 125 and 250 ml amber colored bottles.

Ohio Medical Anesthetics

A Division of Airco, Inc.
3030 Airco Drive, P.O. Box 7550, Madison, Wisconsin 53707
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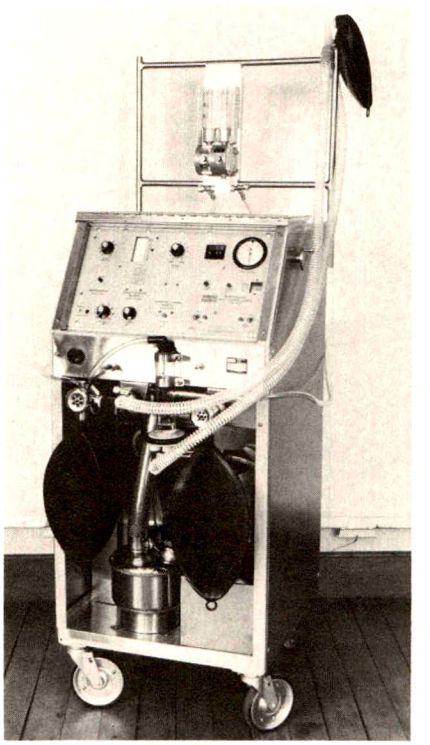
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A MAJOR ADVANTAGE

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Inspiratory flow starts slowly, increases to maximum at mid-breath, and slows down again to a kind of plateau at the end.

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Exhalation is exceptionally free. Thus, the positive phase is not prolonged needlessly, and impact on the cardiovascular system is minimized.

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With characteristics that ensure ventilatory capacity and a minimum of circulatory interference, your Emerson can be called on to treat severely difficult cases. It can provide important benefits in routine cases as well.

*Sullivan, Saklad and Demers: "Ventilator Waveform and Gas Distribution" RESPIRATORY CARE 22:4:393.

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CAMBRIDGE, MASSACHUSETTS 02140

For the response you want,

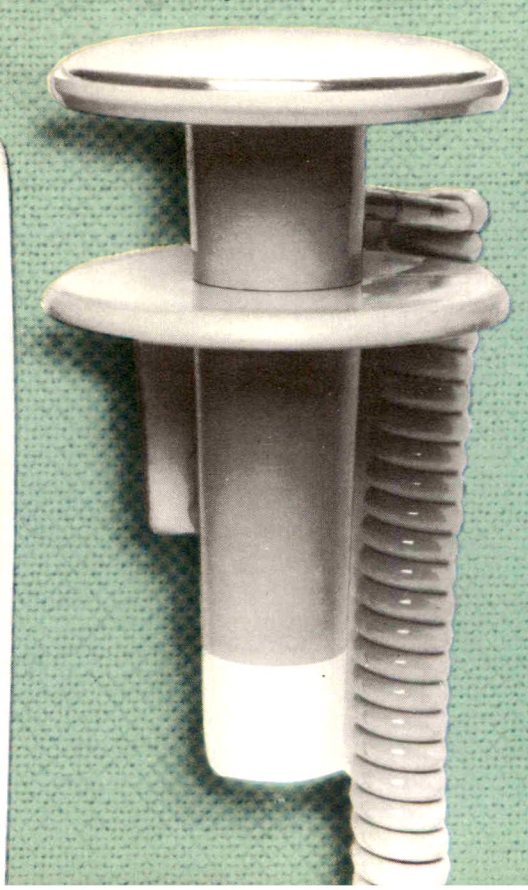
Pre-op

Injectable Valium (diazepam/Roche), administered intramuscularly approximately one hour before surgery, produces the antianxiety response you want. Patients, though calmer, typically remain well-oriented and able to cooperate. When an amnesic effect is desired, intravenous administration just prior to anesthesia produces diminished recall of unpleasant aspects of the induction period. (The dosage of concomitant narcotic analgesics should be reduced by at least one third and in some cases may be omitted.) Since it requires no reconstitution, Injectable Valium is ready immediately.

Pre-procedure

Excessive anxiety in patients facing such procedures as endoscopy or cardioversion can be relieved almost immediately by administering Injectable Valium (diazepam/Roche) I.V. Peak blood levels and expected clinical response are usually achieved in less than 3 minutes. Most patients are greatly relaxed, yet alert enough to respond to directions. And Valium provides the added advantage of predictable anterograde amnesia: usually lasting only 20 to 60 minutes, in sharp contrast to agents producing amnesia for up to 8 hours—sometimes longer. Used appropriately, Injectable Valium seldom significantly alters vital signs. It should be administered with caution to the elderly, the very ill and to patients with limited pulmonary reserve. Resuscitative facilities should be readily available.





Please see summary of product information on following page.

the control you need.

Post-op

Offering I.M. or I.V. dosage options, Injectable Valium (diazepam/Roche) can be especially useful in patients who cannot take medication by mouth during the postoperative period. Its pronounced calming action relieves the excessive anxiety that can not only complicate the recovery process, but often intensifies pain perception. Used adjunctively, Injectable Valium also helps to relieve painful skeletal muscle spasm, frequently seen in the postsurgical patient.

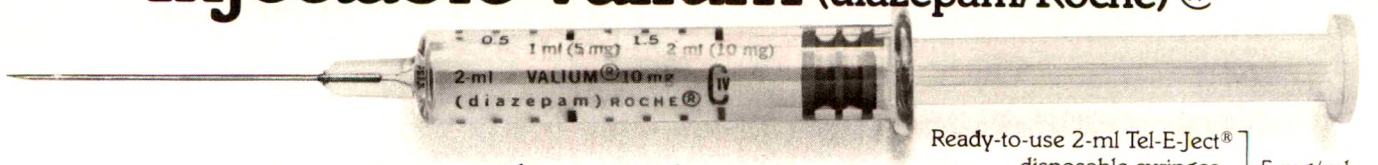
Injectable Valium® I.M./I.V.

diazepam/Roche ℞

Unquestionably the choice.



Injectable Valium® (diazepam/Roche) ℞



Ready-to-use 2-ml Tel-E-Ject® disposable syringes
2-ml ampuls, 10-ml vials
} 5 mg/ml

versatile . . . and predictable

- prompt control of anxiety/apprehension
- anterograde amnesia of brief duration
- effective adjunctive skeletal muscle relaxant
- useful in outpatients as well as inpatients

Please consult complete product information, a summary of which follows:

Indications: Management of anxiety disorders, or short-term relief of symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic. Symptomatic relief of acute agitation, tremor, impending or acute delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in: relief of skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; tetanus; status epilepticus, severe recurrent seizures; adjunctively in anxiety, tension or acute stress reactions prior to endoscopic/surgical procedures; cardioversion.

Contraindications: Hypersensitivity; acute narrow angle glaucoma; may be used in paitents with open angle glaucoma receiving appropriate therapy.

Warnings: *To reduce the possibility of venous thrombosis, phlebitis, local irritation, swelling, and, rarely, vascular impairment when used I.V.: inject slowly, taking at least one minute for each 5 mg (1 ml) given; do not use small veins,* i.e., *dorsum of hand or wrist; use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute Valium (diazepam/Roche) with other solutions or drugs in syringe or infusion flask. If it is not feasible to administer Valium directly I.V., it may be injected slowly through the infusion tubing as close as possible to the vein insertion.*

Administer with extreme care to elderly, very ill, those with limited pulmonary reserve because of possibility of apnea and/or cardiac arrest; concomitant use of barbiturates, alcohol or other CNS depressants increases depression with increased risk of apnea; have resuscitative facilities available. When used with narcotic analgesic, eliminate or reduce narcotic dosage at least ⅓, administer in small increments. Should not be administered to patients in shock, coma, acute alcoholic intoxication with depression of vital signs. As with most CNS-acting drugs, caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).

Has precipitated tonic status epilepticus in patients treated for petit mal status or petit mal variant status.

Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation after long use of excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after long, continuous use at high therapeutic levels. After extended therapy, gradually taper dosage.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations, as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Not recommended for OB use.

Efficacy/safety not established in neonates (age 30 days or less); prolonged CNS depression observed. In children, give slowly (up to 0.25 mg/kg over 3 minutes) to avoid apnea or prolonged somnolence; can be repeated after 15 to 30 minutes. If no relief after third administration, appropriate adjunctive therapy is recommended.

Precautions: Although promptly controlled, seizures may return; readminister if necessary; not recommended for long-term maintenance therapy.

If combined with other psychotropics or anticonvulsants, carefully consider individual pharmacologic effects—particularly with known compounds which may potentiate action of Valium (diazepam/Roche), *i.e.*, phenothiazines, narcotics, barbiturates, MAO inhibitors, antidepressants. Protective measures indicated in highly anxious patients with accompanying depression who may have suicidal tendencies. Observe usual precautions in impaired hepatic function; avoid accumulation in patients with compromised kidney function. Laryngospasm/increased cough reflex are possible during peroral endoscopic procedures; use topical anesthetic, have necessary countermeasures available. Hypotension or muscular weakness possible, particularly when used with narcotics, barbiturates or alcohol. Use lower doses (2 to 5 mg) for elderly/debilitated.

The clearance of Valium and certain other benzodiazepines can be delayed in association with Tagamet (cimetidine) administration. The clinical significance of this is unclear.

Adverse Reactions: Drowsiness, fatigue, ataxia, venous thrombosis/phlebitis at injection site, confusion, depression, dysarthria, headache, hypoactivity, slurred speech, syncope, tremor, vertigo, constipation, nausea, incontinence, changes in libido, urinary retention, bradycardia, cardiovascular collapse, hypotension, blurred vision, diplopia, nystagmus, urticaria, skin rash, hiccups, changes in salivation, neutropenia, jaundice. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Cough, depressed respiration, dyspnea, hyperventilation, laryngospasm/pain in throat and chest have been reported in peroral endoscopic procedures. Isolated reports of neutropenia, jaundice; periodic blood counts, liver function tests advisable during long-term therapy. Minor EEG changes, usually low-voltage fast activity, of no known significance.

Dosage: Usual initial dose in older children and adults is 2 to 20 mg I.M. or I.V., depending on indication and severity. Larger doses may be required in some conditions (tetanus). In acute conditions injection may be repeated within 1 hour, although interval of 3 to 4 hours is usually satisfactory. Lower doses (usually 2 to 5 mg) with slow dosage increase for elderly or debilitated patients and when sedative drugs are added. (See Warnings and Adverse Reactions.)

For dosages in infants and children see below; have resuscitative facilities available.

I.M. use: by deep injection into the muscle.

I.V. use: inject slowly, take at least one minute for each 5 mg (1 ml) given. Do not use small veins, i.e., *dorsum of hand or wrist. Use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute Valium (diazepam/Roche) with other solutions or drugs in syringe or infusion flask. If it is not feasible to administer Valium directly I.V., it may be injected slowly through the infusion tubing as close as possible to the vein insertion.*

Moderate anxiety disorders and symptoms of anxiety, 2 to 5 mg I.M. or I.V. and severe anxiety disorders and symptoms of anxiety, 5 to 10 mg I.M. or I.V., repeat in 3 to 4 hours if necessary; acute alcoholic withdrawal, 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary. Muscle spasm, in adults, 5 to 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary (tetanus may require larger doses); in children, *administer I.V. slowly;* for tetanus in infants over 30 days of age, 1 to 2 mg I.M. or I.V., repeat every 3 to 4 hours if necessary; in children 5 years or older, 5 to 10 mg repeated every 3 to 4 hours as needed. Respiratory assistance should be available.

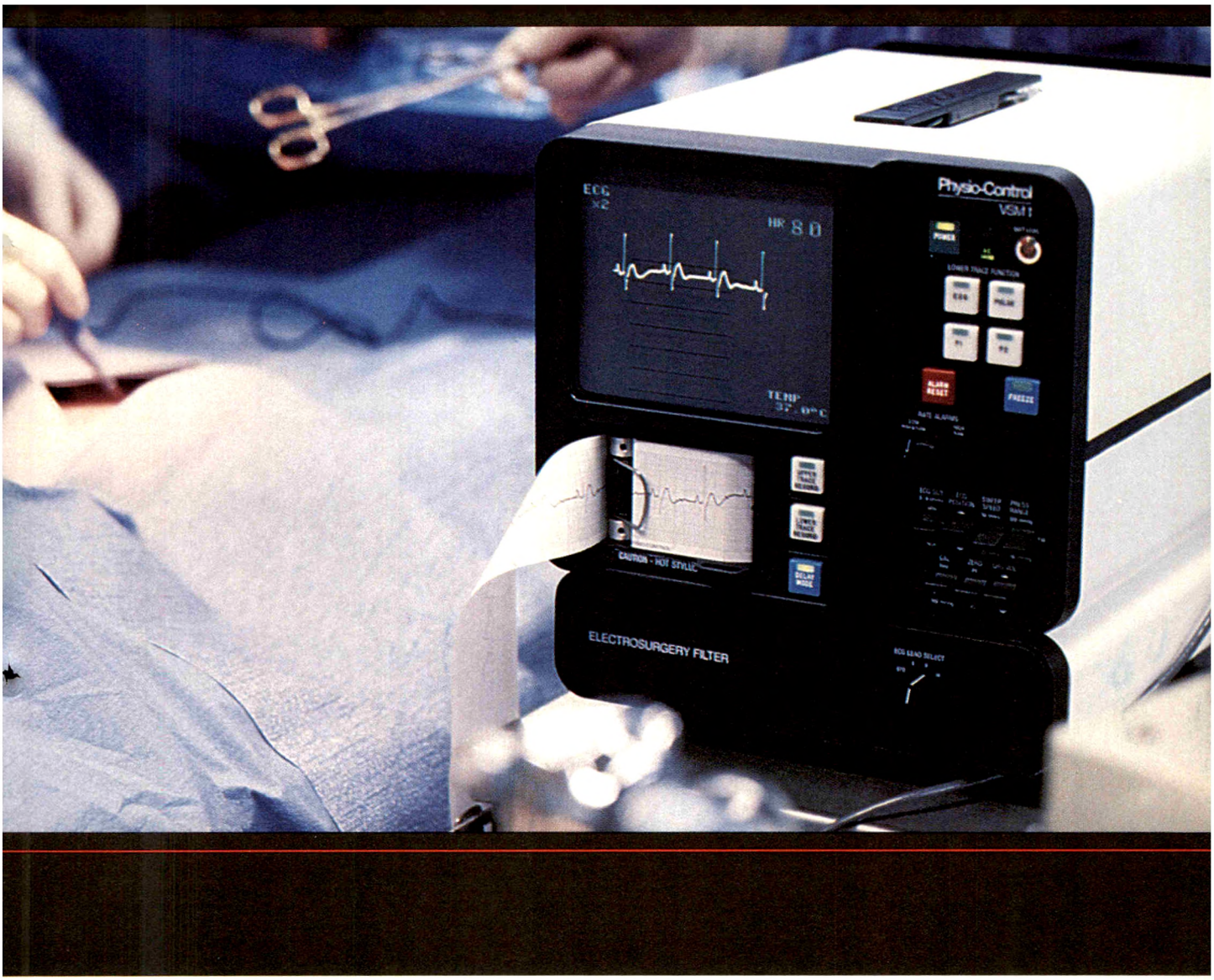
Status epilepticus, severe recurrent convulsive seizures (I.V. route preferred), 5 to 10 mg adult dose administered slowly, repeat at 10- to 15-minute intervals up to 30 mg maximum. Repeat in 2 to 4 hours if necessary keeping in mind possibility of residual active metabolites. Use caution in presence of chronic lung disease or unstable cardiovascular status. Infants (over 30 days) and children (under 5 years), 0.2 to 0.5 mg slowly every 2 to 5 min., up to 5 mg (I.V. preferred). Children 5 years plus, 1 mg every 2 to 5 min., up to 10 mg (slow I.V. preferred); repeat in 2 to 4 hours if needed. EEG monitoring may be helpful.

In endoscopic procedures, titrate I.V. dosage to desired sedative response, generally 10 mg or less but up to 20 mg (if narcotics are omitted) immediately prior to procedure; if I.V. cannot be used, 5 to 10 mg I.M. approximately 30 minutes prior to procedure. As preoperative medication, 10 mg I.M.; in cardioversion, 5 to 15 mg I.V. within 5 to 10 minutes prior to procedure. Once acute symptomatology has been properly controlled with injectable form, patient may be placed on oral form if further treatment is required.

Management of Overdosage: Manifestations include somnolence, confusion, coma, diminished reflexes. Monitor respiration, pulse, blood pressure; employ general supportive measures, I.V. fluids, adequate airway. Hypotension may be combated by the use of levarterenol or metaraminol. Dialysis is of limited value.

Supplied: Ampuls, 2 ml, boxes of 10; Vials, 10 ml, boxes of 1; Tel-E-Ject® (disposable syringes), 2 ml, boxes of 10. Each ml contains 5 mg diazepam compounded with 40% propylene glycol, 10% ethyl alcohol, 5% sodium benzoate and benzoic acid as buffers, and 1.5% benzyl alcohol as preservative.

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Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110



Physio-Control announces a clearly superior answer to monitoring during electrosurgery.

The photo above was taken during routine electrosurgery. The clear trace is made possible by our new electrosurgical filter (ESF)—now available as an option for the Physio-Control VSM™1 Vital Signs Monitor. With the new ESF module, there is almost no perceptable degradation of ECG wave forms even at high power settings. Seeing is believing, of course, but we are confident that our new ESF module is *clearly* superior to any other filter on the market. For a demonstration, contact your nearest Physio-Control representative.

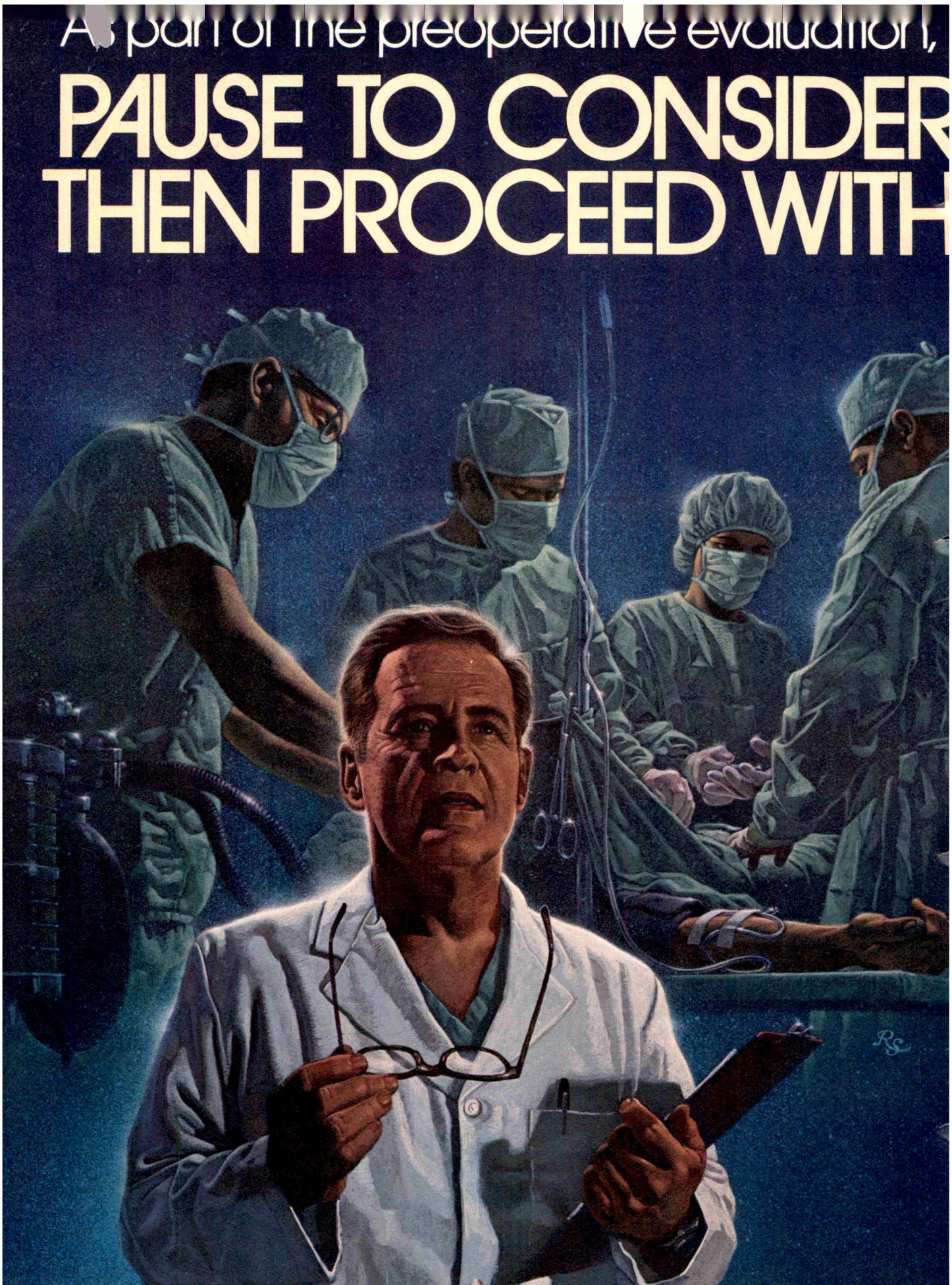
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The VSM1 Vital Signs Monitor from Physio-Control.

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As part of the preoperative evaluation I,
PAUSE TO CONSIDER
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THE RECORD,
PAVULON® nondepolarizing muscle relaxant (pancuronium bromide injection)

Pavulon was introduced into the United States after four years of documented success in Europe.

Now, after more than a decade, the Pavulon record of superior performance, efficacy and safety continues.

Pavulon has been used successfully in a wide variety of surgical procedures involving all patient types—from the neonate to the elderly—from the poor risk patient to the good risk patient. In addition, Pavulon has proved a valuable adjunct in the management of mechanically ventilated patients in intensive care units.

A Record of Success
PAVULON®
(pancuronium bromide injection)

Please see next page for brief summary of prescribing information.

Organon
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Organon Pharmaceuticals
A Division of Organon Inc.
West Orange, N.J. 07052

OR-2966

A Record of Success

PAVULON® nondepolarizing muscle relaxant (pancuronium bromide injection)

BRIEF SUMMARY
(Please consult package insert for full prescribing information.)

THIS DRUG SHOULD ONLY BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

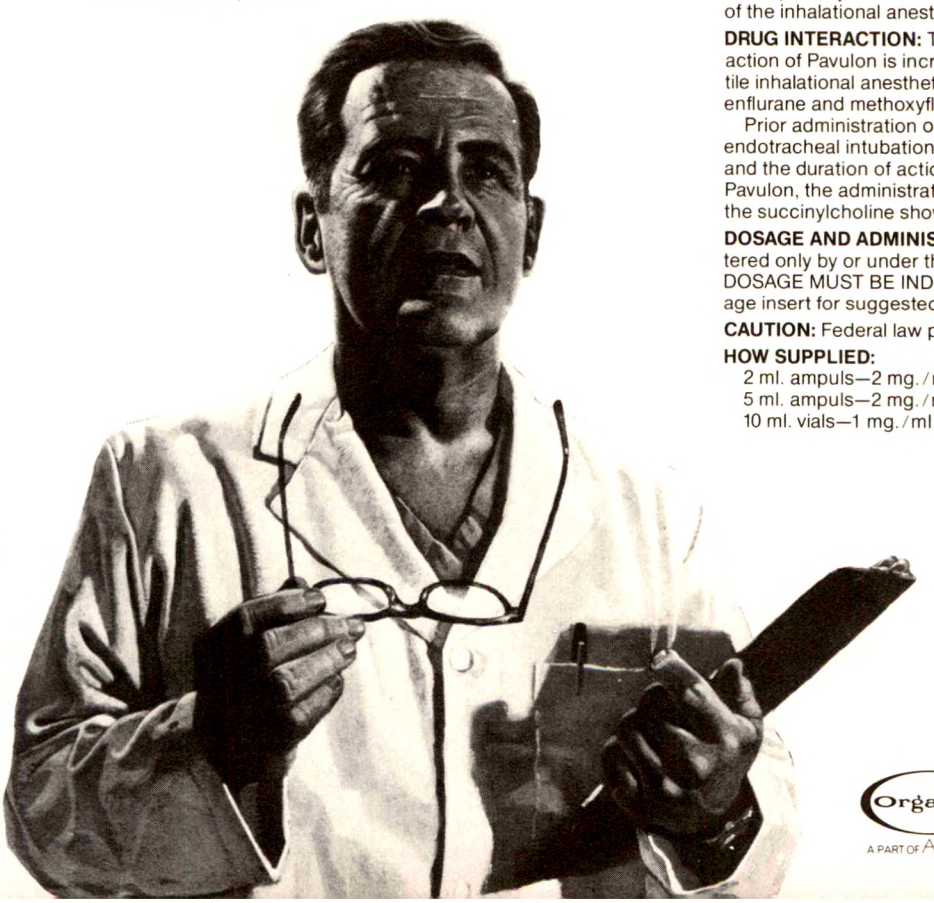
ACTIONS: Pavulon is a non-depolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform) on the myoneural junction.

Pavulon (pancuronium bromide) is antagonized by acetylcholine, anticholinesterases, and potassium ion. Its action is increased by inhalational anesthetics such as halothane, diethyl ether, enflurane and methoxyflurane, as well as quinine, magnesium salts, hypokalemia, some carcinomas, and certain antibiotics such as neomycin, streptomycin, clindamycin, kanamycin, gentamicin and bacitracin. The action of Pavulon may be altered by dehydration, electrolyte imbalance, acid-base imbalance, renal disease, and concomitant administration of other neuromuscular agents.

CONTRAINDICATIONS: Pavulon is contraindicated in patients known to be hypersensitive to the drug or to the bromide ion.

WARNINGS: PAVULON SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS, WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION.

In patients who are known to have myasthenia gravis small doses of Pavulon may have profound effects. A peripheral nerve stimulator is especially valuable in assessing the effects of Pavulon in such patients.



USAGE IN PREGNANCY: The safe use of pancuronium bromide has not been established with respect to the possible adverse effects upon fetal development. Therefore, it should not be used in women of childbearing potential and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the unknown hazards.

Pavulon may be used in operative obstetrics (Cesarean section), but reversal of pancuronium may be unsatisfactory in patients receiving magnesium sulfate for toxemia of pregnancy, because magnesium salts enhance neuromuscular blockade. Dosage should usually be reduced, as indicated, in such cases.

PRECAUTIONS: Although Pavulon has been used successfully in many patients with pre-existing pulmonary, hepatic, or renal disease, caution should be exercised in these situations. This is particularly true of renal disease since a major portion of administered Pavulon is excreted unchanged in the urine.

ADVERSE REACTIONS: Neuromuscular: the most frequently noted adverse reactions consist primarily of an extension of the drug's pharmacological actions beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle relaxation resulting in respiratory insufficiency or apnea. Inadequate reversal of the neuromuscular blockade by anticholinesterase agents has also been observed with Pavulon (pancuronium bromide) as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate.

Cardiovascular: A slight increase in pulse rate is frequently noted.

Gastrointestinal: Salivation is sometimes noted during very light anesthesia, especially if no anticholinergic premedication is used.

Skin: An occasional transient rash is noted accompanying the use of Pavulon.

Respiratory: One case of wheezing, responding to deepening of the inhalational anesthetic, has been reported.

DRUG INTERACTION: The intensity of blockade and duration of action of Pavulon is increased in patients receiving potent volatile inhalational anesthetics such as halothane, diethyl ether, enflurane and methoxyflurane.

Prior administration of succinylcholine, such as that used for endotracheal intubation, enhances the relaxant effect of Pavulon and the duration of action. If succinylcholine is used before Pavulon, the administration of Pavulon should be delayed until the succinylcholine shows signs of wearing off.

DOSAGE AND ADMINISTRATION: Pavulon should be administered only by or under the supervision of experienced clinicians. DOSAGE MUST BE INDIVIDUALIZED IN EACH CASE. See package insert for suggested dosages.

CAUTION: Federal law prohibits dispensing without prescription.

HOW SUPPLIED:
2 ml. ampuls—2 mg./ml.—boxes of 25, NDC # 0052-0444-26
5 ml. ampuls—2 mg./ml.—boxes of 25, NDC # 0052-0444-25
10 ml. vials—1 mg./ml.—boxes of 25, NDC # 0052-0443-25

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SIEMENS



Servo Humidifier

Servo Humidifier is a new unique self-regulating hygroscopic humidifier for adults and children in anesthesia and intensive care. It is capable of maintaining 100% RH at 33°C (corresponding to ca 80% RH at 37°C) in the trachea of mechanically ventilated patients. The corresponding figure for most heat and moisture exchangers is 55%.

The hygroscopic Servo Humidifier can be used with all mechanical ventilators and most anesthesia gas machines. It is available in two sizes; for adults and children. And it is less expensive than the water in conventional bubble humidifiers!

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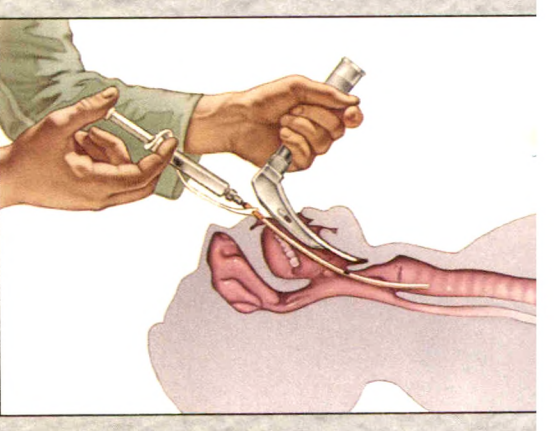
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S-171 95 Solna, Sweden

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the anesthetic of choice, in the only kit that gives you a choice

Introducing the DUO-TRACH

Delivers the laryngotracheal anesthetic of choice, Xylocaine® the original lidocaine HCl solution

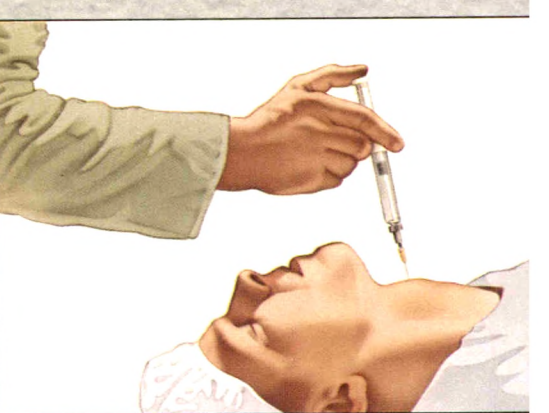
☐ The Xylocaine name is your assurance of quality and effectiveness.



Lets you choose the intraoral or transtracheal route of administration

☐ The anatomically curved cannula provided, conveniently allows administration via the intraoral approach.

☐ For transtracheal injection, simply discard the cannula and attach the needle of your choice. Most needles adapt themselves readily to the luer fitting.



10 jets ATOP cannula
- upward spray ensures 360° coverage
- jets evenly positioned for full coverage of larynx and trachea

Guide mark
- a convenient indicator for proper positioning during use

Terminal jet
- covers tracheo-bronchial junction



KIT

A sterile, disposable, prefilled syringe and cannula kit for convenient laryngotracheal anesthesia prior to intubation, diagnosis, surgery.



25% more drug than other kits*

- contains 5ml Xylocaine® (lidocaine HCl) 4% Solution to allow for greater range of dosage determination

Calibrated barrel

- marked in 1/2 ml increments to aid in proper dose determination and accuracy of drug delivery

Prefilled syringe

- totally sterile and self-contained
- no vial to insert, no risk of contamination

Hub guard

- a simple twist quickly activates the syringe and readies the unit for attachment of cannula or needle

Luer hub

- firmly secures needle or cannula

Safety strap

- an extra precaution against inadvertent cannula disengagement

Separate syringe unit

- lets you choose either intraoral or transtracheal routes of administration at your discretion

Cannula

- anatomically curved to facilitate introduction into larynx and trachea.
- easily attaches to syringe, virtually no assembly time

*Although absorption of lidocaine from respiratory mucosa varies widely among individuals, blood concentrations achieved by this route can rise to levels comparable to those reached by similar doses infused intravenously, and in some cases almost as rapidly.[1,2,3]

REFERENCES

1. Bromage P: Concentrations of lidocaine in the blood after intravenous and endotracheal administration. *Anaesthesia*, 16:461, 1961.
2. Chu S: Plasma concentration of lidocaine after endotracheal spray. *Anesth. Analg.*, 54:438, 1975.
3. Pelton D: Plasma lidocaine concentrations following topical aerosol application to the trachea and bronchi. *Canad. Anaesth. Soc. J.*, 17:250, 1970.

ASTRA®

Astra Pharmaceutical Products, Inc.
Worcester, Massachusetts 01606

(Please see following page for a brief summary of prescribing information.)

Xylocaine®
(lidocaine hydrochloride)
4% Sterile Solution

Before prescribing or administering, please consult complete product information, a summary of which follows:

CONTRAINDICATIONS: Lidocaine hydrochloride sterile solution is contraindicated in patients with a known history of hypersensitivity either to local anesthetics of the amide type or to other components of the sterile solution.

PRECAUTIONS: The safety and effectiveness of lidocaine hydrochloride depend on proper dosage, correct technique, adequate precautions, and readiness for emergencies. Standard textbooks should be consulted for specific techniques and precautions for various anesthetic procedures.

The lowest dosage that results in effective anesthesia should be used. Injection of repeated doses of lidocaine hydrochloride may cause significant increases in blood levels with each repeated dose due to slow accumulation of the drug or its metabolites. Tolerance varies with the status of the patient. Debilitated, elderly patients, acutely ill patients, and children should be given reduced doses commensurate with their age and physical status. Lidocaine hydrochloride should also be used with caution in patients with severe shock or heart block.

As with all injections of local anesthetics, retrobulbar injection should always be made slowly and with frequent aspirations.

Solutions to which a vasoconstrictor has been added should be used with caution in the presence of diseases which may adversely affect the patient's cardiovascular system. Serious cardiac arrhythmias may occur if preparations containing a vasoconstrictor are employed in patients during or following the administration of chloroform, halothane, cyclopropane, trichlorethylene, or other related agents.

Lidocaine hydrochloride should be used with caution in persons with known drug sensitivities. Patients allergic to para-aminobenzoic acid derivatives (procaine, tetracaine, benzocaine, etc.) have not shown cross sensitivity to lidocaine HCl.

Local anesthetics react with certain metals and cause the release of their respective ions which, if injected, may cause severe local irritation. Adequate precaution should be taken to avoid this type of interaction.

The safety of amide local anesthetics in patients with malignant hyperthermia has not been assessed, and therefore, those agents should be used with caution in such patients.

Drowsiness following lidocaine hydrochloride injection is *usually* an early indication of a high blood level of the drug and may occur following inadvertent intravascular administration or *rapid absorption* of lidocaine.

ADVERSE REACTIONS: Adverse reactions may result from high plasma levels due to excessive dosage, rapid absorption or inadvertent intravascular injection. Such reactions are systemic in nature and involve the central nervous system and/or the cardiovascular system. A small number of reactions may result from hypersensitivity, idiosyncrasy or diminished tolerance on the part of the patient.

CNS reactions are excitatory and/or depressant, and may be characterized by nervousness, dizziness, blurred vision and tremors, followed by drowsiness, convulsions, unconsciousness and possibly respiratory arrest. The excitatory reactions may be very brief or may not occur at all, in which case the first manifestations of toxicity may be drowsiness, merging into unconsciousness and respiratory arrest.

Toxic cardiovascular reactions to local anesthetics are usually depressant in nature and are characterized by hypotension, myocardial depression, bradycardia and possibly cardiac arrest.

Treatment of a patient with toxic manifestations consists of assuring and maintaining a patent airway, supporting ventilation with oxygen, and assisted or controlled ventilation (respiration) as required. This usually will be sufficient in the management of most reactions. Should a convulsion persist despite ventilation therapy, small increments of anticonvulsive agents may be given intravenously. Examples of such agents include benzodiazepine (e.g., diazepam), ultrashort acting barbiturates (e.g., thiopental or thiamylal) or a short acting barbiturate (e.g., pentobarbital or secobarbital). Cardiovascular depression may require circulatory assistance with intravenous fluids and/or vasopressors (e.g., ephedrine) as dictated by the clinical situation.

Allergic reactions may occur as a result of sensitivity either to local anesthetics or to other components of the sterile solution. Anaphylactoid type symptomatology and reactions, characterized by cutaneous lesions, urticaria, edema, should be managed by conventional means. The detection of potential sensitivity by skin testing is of limited value.

HOW SUPPLIED: Xylocaine (lidocaine hydrochloride) 4% Sterile Solution:
5 ml ampule, package of 10; 5 ml prefilled sterile disposable syringe.

ASTRA®
Astra Pharmaceutical Products, Inc.
Worcester, Massachusetts 01606

ADDRESS CHANGE NOTICE

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Only one premedicant does so many things so well



- **Provides prompt tranquilization**
- **Inhibits emesis during and after surgery**
- **Contributes to cardiovascular stability**

  Unique among premedicants, INAPSINE® (droperidol) provides vasodilation and mild alpha-adrenergic blocking effects which can help protect against undue hypertensive reactions and changes in heart rate.
  Troublesome hypotension is unlikely in the absence of hypovolemia. Has little or no adverse effect on the heart or circulation.
- **Reduces the need for postoperative narcotics**

A PROFILE OF CHARACTERISTICS UNMATCHED BY ANY OTHER SINGLE AGENT

	Inapsine® (droperidol) Injection	Diazepam Injection	Lorazepam Injection	Hydroxy-zine Injection
Class of tranquilizer	**Major**	Minor	Minor	Minor
Elimination half-life	**2.3 hrs.**	27-37 hrs.	16 hrs.	3-4 hrs.
Antiemetic activity	**Signifi-cant**	No	No	Mild
Alpha-adrenergic blockade	**YES**	No	No	No
May be used both IM and IV	**YES**	Yes (IM preferred)	Yes	No
Less pain on injection	**YES**	No	No	No
Same syringe compatibility with atropine, scopolamine	**YES**	No	No	Yes

Please see brief summary of Prescribing Information on next page.

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A premedicant that does more than premedicate

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Janssen Pharmaceutica Inc, 501 George St., New Brunswick, N.J. 08903

Inapsine®
(droperidol) Injection

Inapsine® (droperidol) Injection ℞

Before prescribing please consult complete prescribing information, of which the following is a brief summary.

DESCRIPTION:
2 ml. and 5 ml. ampoules
Each ml. contains:
Droperidol . . . . . 2.5 mg.
Lactic acid for pH adjustment to 3.4 ± 0.4
10 ml. vials
Each ml. contains:
Droperidol . . . . . 2.5 mg.
With 1.8 mg. methylparaben and 0.2 mg. propylparaben, and lactic acid for pH adjustment to 3.4 ± 0.4.
Protect from light. Store at room temperature.
FOR INTRAVENOUS OR INTRAMUSCULAR USE ONLY
Droperidol is a neuroleptic (tranquilizer) agent.

INDICATIONS: INAPSINE (droperidol) is indicated:
to produce tranquilization and to reduce the incidence of nausea and vomiting in surgical and diagnostic procedures;
for premedication, induction, and as an adjunct in the maintenance of general and regional anesthesia;
in neuroleptanalgesia in which INAPSINE (droperidol) is given concurrently with a narcotic analgesic, such as SUBLIMAZE® (fentanyl) injection, to aid in producing tranquility and decreasing anxiety and pain.

CONTRAINDICATIONS: INAPSINE (droperidol) is contraindicated in patients with known intolerance to the drug.

WARNINGS: FLUIDS AND OTHER COUNTERMEASURES TO MANAGE HYPOTENSION SHOULD BE READILY AVAILABLE. As with other CNS depressant drugs, patients who have received INAPSINE (droperidol) should have appropriate surveillance.
If INAPSINE (droperidol) is administered with a narcotic analgesic such as SUBLIMAZE (fentanyl), the user should familiarize himself with the special properties of each drug, particularly the widely differing durations of action. In addition, when such a combination is used, resuscitative equipment and a narcotic antagonist should be readily available to manage apnea. See package insert for fentanyl before using. Narcotic analgesics such as SUBLIMAZE (fentanyl) may cause muscle rigidity, particularly involving the muscles of respiration. This effect is related to the speed of injection. Its incidence can be reduced by the use of slow intravenous injection. Once this effect occurs, it is managed by the use of assisted or controlled respiration and, if necessary, by a neuromuscular blocking agent compatible with the patient's condition.
The respiratory depressant effect of narcotics persists longer than their measured analgesic effect. When used with INAPSINE (droperidol), the total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, be used initially in reduced doses as low as ¼ to ⅓ those usually recommended.

PRECAUTIONS: The initial dose of INAPSINE (droperidol) should be appropriately reduced in elderly, debilitated and other poor-risk patients. The effect of the initial dose should be considered in determining incremental doses. Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can cause peripheral vasodilatation and hypotension because of sympathetic blockade. Through other mechanisms INAPSINE (droperidol) can also alter circulation. Therefore, when INAPSINE (droperidol) is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for this form of anesthesia.
If hypotension occurs, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should also be considered when operative conditions permit. It should be noted that in spinal and peridural anesthesia, tilting the patient into a head down position may result in a higher level of anesthesia than is desirable, as well as impair venous return to the heart. Care should be exercised in moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do not correct the hypotension, then the administration of pressor agents other than epinephrine should be considered. Epinephrine may paradoxically decrease the blood pressure in patients treated with INAPSINE (droperidol) due to the alpha-adrenergic blocking action of droperidol.
Since INAPSINE (droperidol) may decrease pulmonary arterial pressure, this fact should be considered by those who conduct diagnostic or surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient. Vital signs should be monitored routinely.
Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, and general anesthetics) have additive or potentiating effects with INAPSINE (droperidol). When patients have received such drugs, the dose of INAPSINE (droperidol) required will be less than usual. Likewise, following the administration of INAPSINE (droperidol), the dose of other CNS depressant drugs should be reduced.
INAPSINE (droperidol) should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.
When the EEG is used for postoperative monitoring, it may be found that the EEG pattern returns to normal slowly.
Since INAPSINE (droperidol) is frequently used with the narcotic analgesic SUBLIMAZE (fentanyl), it should be noted that fentanyl may produce bradycardia, which may be treated with atropine; however, fentanyl should be used with caution in patients with cardiac bradyarrhythmias.*

ADVERSE REACTIONS: The most common adverse reactions reported to occur with INAPSINE (droperidol) are mild to moderate hypotension and occasionally tachycardia, but these effects usually subside without treatment. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Postoperative drowsiness is also frequently reported.
Extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed following administration of INAPSINE (droperidol). Restlessness, hyperactivity, and anxiety which can be either the result of inadequate dosage of INAPSINE (droperidol) or a part of the symptom complex of akathisia may occur. When extrapyramidal symptoms occur, they can usually be controlled with anti-parkinson agents.
Other adverse reactions that have been reported are dizziness, chills and/or shivering, laryngospasm, bronchospasm and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression).
When INAPSINE (droperidol) is used with a narcotic analgesic such as SUBLIMAZE (fentanyl), respiratory depression, apnea, and muscular rigidity can occur; if these remain untreated respiratory arrest could occur. Elevated blood pressure, with or without preexisting hypertension, has been reported following administration of INAPSINE (droperidol) combined with SUBLIMAZE (fentanyl) or other parenteral analgesics. This might be due to unexplained alterations in sympathetic activity following large doses; however, it is also frequently attributed to anesthetic or surgical stimulation during light anesthesia.

DOSAGE AND ADMINISTRATION: Dosage should be individualized. Some of the factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and the surgical procedure involved. Vital signs should be monitored routinely.

Usual Adult Dosage

I. Premedication—(to be appropriately modified in the elderly, debilitated, and those who have received other depressant drugs) 2.5 to 10 mg. (1 to 4 ml.) may be administered intramuscularly 30 to 60 minutes preoperatively.

II. Adjunct to General Anesthesia
Induction—2.5 mg. (1 ml.) per 20 to 25 pounds may be administered (usually intravenously) along with an analgesic and/or general anesthetic. Smaller doses may be adequate. The total amount of INAPSINE (droperidol) administered should be titrated to obtain the desired effect based on the individual patient's response.
Maintenance—1.25 to 2.5 mg. (0.5 to 1 ml.) usually intravenously (see warning regarding use with concomitant narcotic analgesic medication and the possibility of widely differing durations of action).
If INNOVAR® injection is administered in addition to INAPSINE (droperidol), the calculation of the recommended dose of INAPSINE (droperidol) should include the droperidol contained in the INNOVAR injection. See INNOVAR injection Package Insert for full prescribing information.

III. Use Without A General Anesthetic In Diagnostic Procedures—Administer the usual I.M. premedication 2.5 to 10 mg. (1 to 4 ml.) 30 to 60 minutes before the procedure. Additional 1.25 to 2.5 mg. (0.5 to 1 ml.) amounts of INAPSINE (droperidol) may be administered, usually intravenously (see warning regarding use with concomitant narcotic analgesic medication and the possibility of widely differing durations of action).
Note: When INAPSINE (droperidol) is used in certain procedures, such as bronchoscopy, appropriate topical anesthesia is still necessary.

IV. Adjunct to Regional Anesthesia—2.5 to 5 mg. (1 to 2 ml.) may be administered intramuscularly or slowly intravenously when additional sedation is required.

HOW SUPPLIED: 2 ml. and 5 ml. ampoules-packages of 10; 10 ml. multiple-dose vials—packages of 10.
U.S. Patent No. 3,161,645
NDC 50458-010-02; NDC 50458-010-05; NDC 50458-010-10

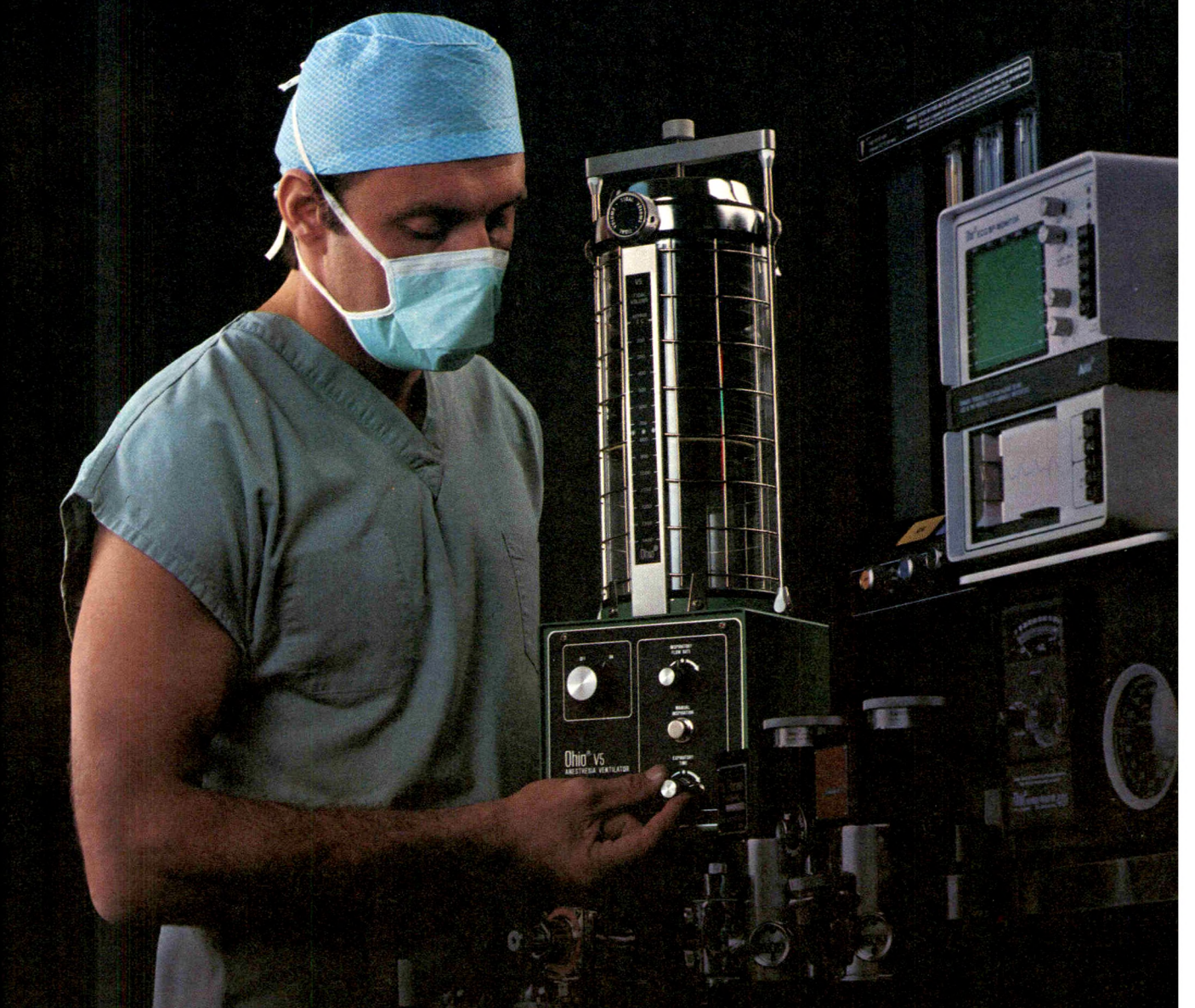
March 1980, Revised June 1980

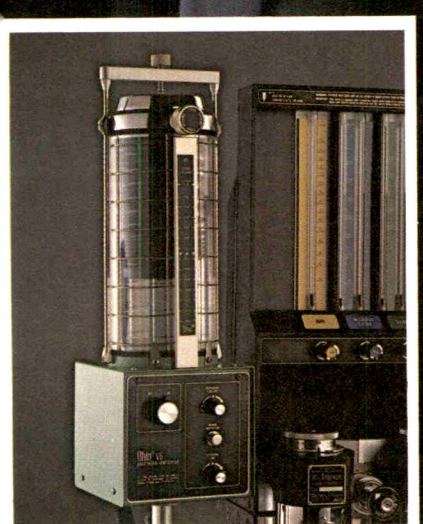
*See full prescribing information for complete description.

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Ohio V5 Ventilator: Simple controls keep you in control.





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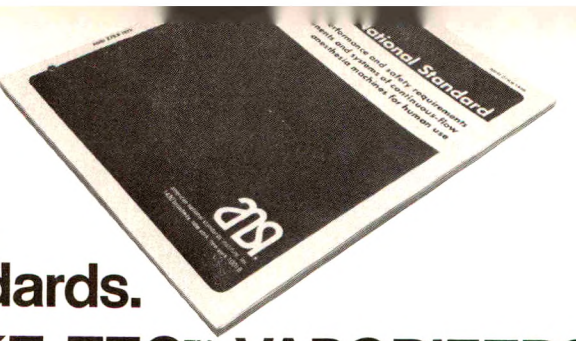
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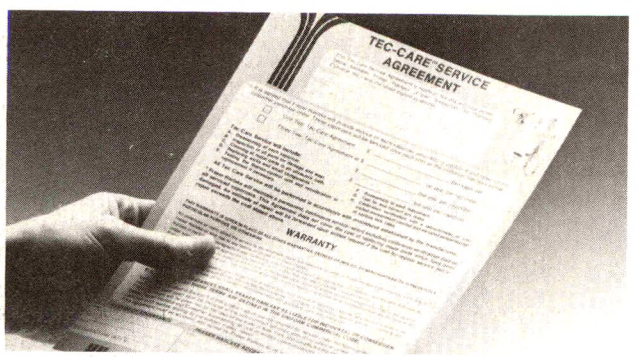
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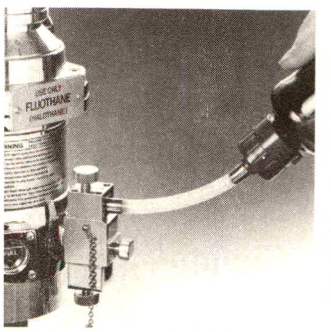
A.N.S.I. Z79 13.1.14 Re: Variance of delivered concentration as affected by temperature.

Introduced in 1958, the Tec vaporizer is the original temperature compensated, agent-specific vaporizer. Tec vaporizers were designed to ensure that the output concentration of anesthetic agent is not affected by temperature variation, flow rate, liquid level, or back pressure fluctuation. Four models: the Fluotec® Mk III, the Pentec® Mk II, the Enfluratec,® and the Fortec,® meet all of the requirements of inhalation anesthesia.



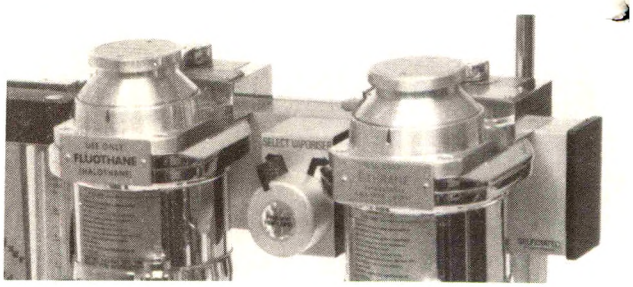
A.N.S.I. Z79 4.1.5 Re: Manufacturer recommendations for periodic service.

Fraser Harlake has provided regular preventive maintenance and service for Tec vaporizers since 1961, offering hospitals an efficient way to maintain vaporizer performance. Annual preventive maintenance, cleaning, calibration verification, and testing provide assurance that each vaporizer is working properly. Fraser Harlake permanently maintains a legally useful continuous service record. In addition, the Tec-Care™ program offers hospitals price protection on vaporizer service.



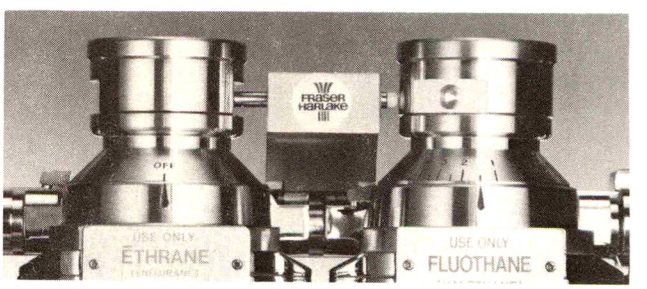
A.N.S.I. Z79 13.1.11 Re: Safeguards in vaporizer filling systems.

Fraser Harlake's widely acknowledged, unique keyed filler system was first marketed in 1968. This extra safety measure ensures that each vaporize is filled only with the drug for which it was originally designed and calibrated.



A.N.S.I. Z79 13.1.4 Re: Mounting systems to prevent drug cross-contamination.

Fraser Harlake's safety innovations continued in 1977 with the development of the Selectatec™ III mounting system Selectatec mounting minimizes cross-contamination of anesthetic drugs and provides an easier method of removing vaporizers for servicing.



For standard Mark III backbar mounted vaporizers, Fraser Harlake offers the new Tecloc™ interlock safety system.

More than 20 years of reliable clinical experience have made the Fraser Harlake Tec vaporizer the industry standard.

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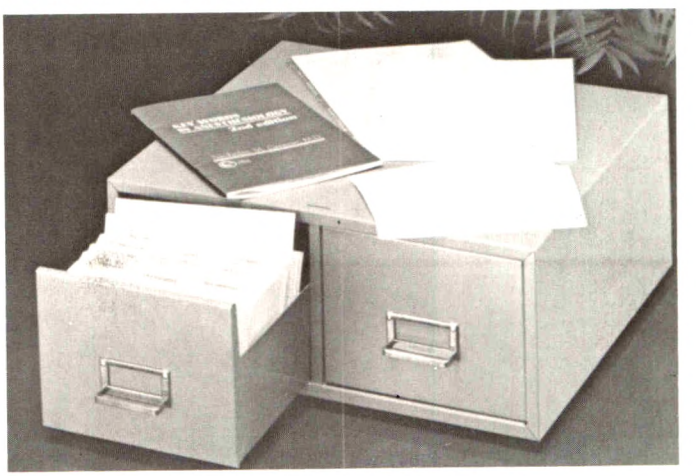
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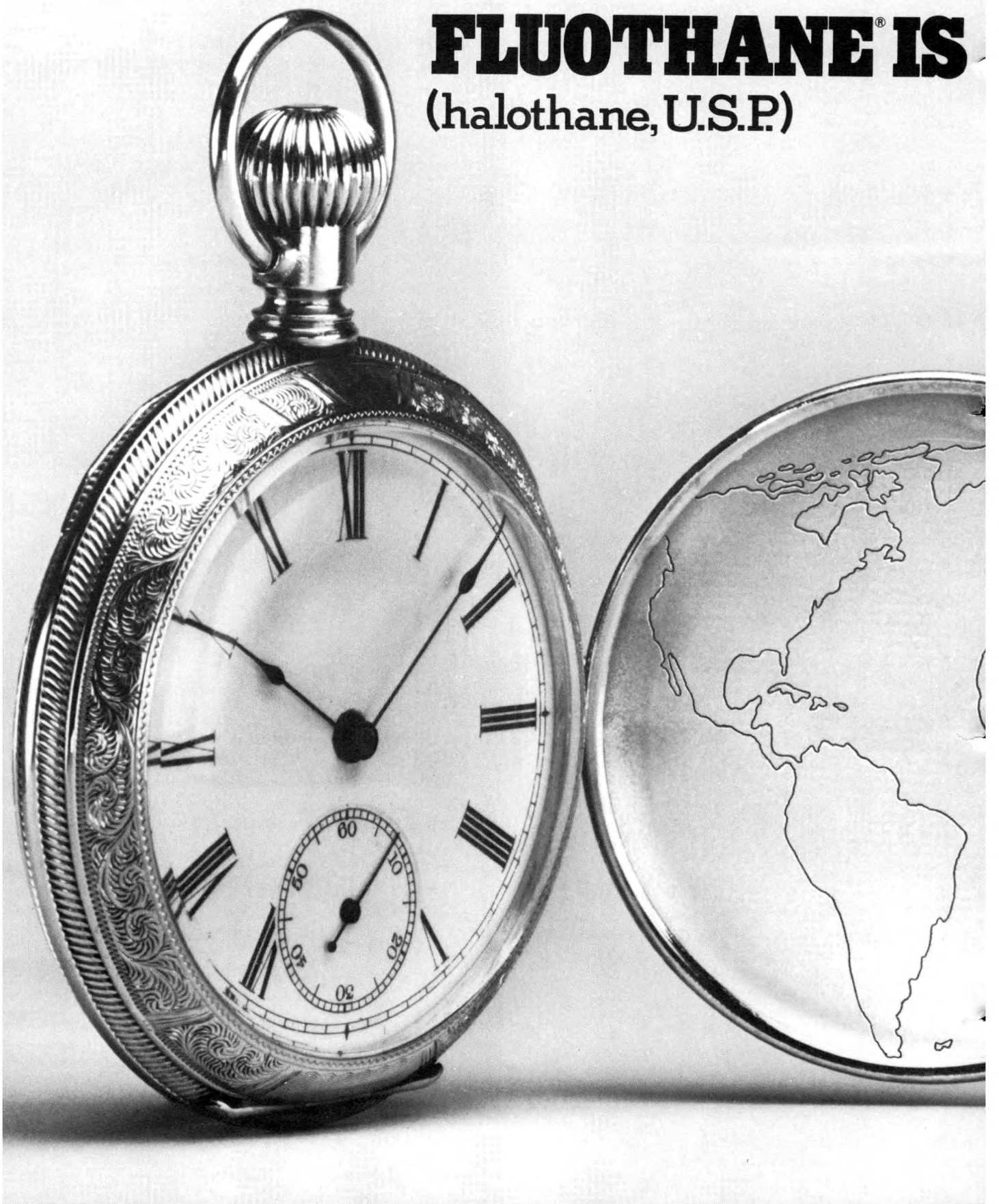
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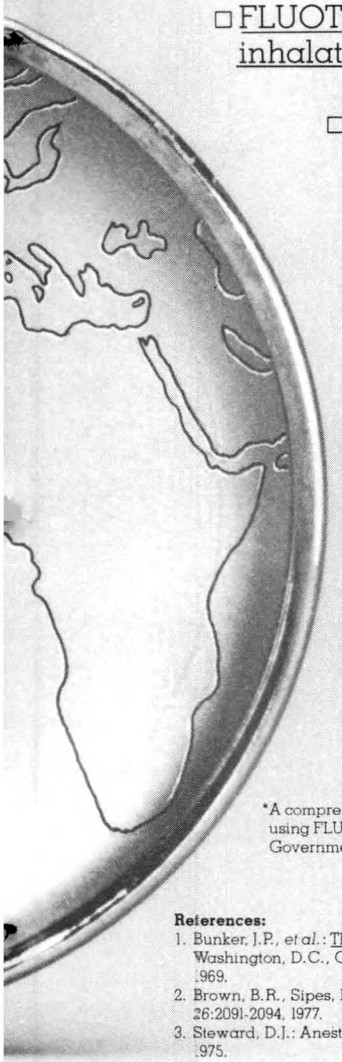
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- FLUOTHANE has been more widely investigated than any other inhalation anesthetic.
- The FLUOTHANE experience shows association with hepatotoxicity to be extremely rare.[1] According to conclusions drawn from the United States National Halothane Study and other studies,* unexplained jaundice following anesthesia with halothane "...was a rare occurrence (approximately 1:30,000 administrations) and...the overall safety record of the anesthetic was excellent."[2]
- FLUOTHANE "...is nearest to the ideal [inhalation anesthetic] presently available for children of all ages."[3]
- FLUOTHANE has been recommended as the "anesthetic of choice"[4] for asthmatics.
- And, of particular benefit in geriatrics and cardiovascular surgery: Excessive respiratory depression is rarely a problem with FLUOTHANE. Nor does it produce an increase in salivary or bronchial secretions.

*A comprehensive retrospective analysis covering 856,000 general anesthesias—nearly one-third using FLUOTHANE. Bunker, J.P., *et al.*: The National Halothane Study. Washington, D.C., Government Printing Office, 1969.

References:

1. Bunker, J.P., *et al.*: The National Halothane Study. Washington, D.C., Government Printing Office, 1969.
2. Brown, B.R., Sipes, I.G.: Biochem. Pharmacol. 26:2091-2094, 1977.
3. Steward, D.J.: Anesthesiology 43:268-276 (Aug.) 1975.
4. Proceedings, Virginia Society of Anesthesiologists, April 20-22, 1979, Richmond, VA.

See following page for Brief Summary.

Ayerst Laboratories
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the most widely used inhalation anesthetic in the world

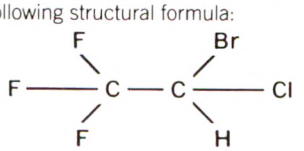
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(Complete text of package circular.)

Description. FLUOTHANE, brand of halothane, U.S.P., is an inhalation anesthetic. It is 2-bromo-2-chloro-1, 1, 1-trifluoroethane and has the following structural formula:



The specific gravity is 1.872-1.877 at 20°C, and the boiling point (range) is 49°C – 51°C at 760 mm Hg. The vapor pressure is 243 mm Hg at 20°C. The blood/gas coefficient is 2.5 at 37°C, and the olive oil/water coefficient is 220 at 37°C. Vapor concentrations within anesthetic range are nonirritating and have a pleasant odor. FLUOTHANE is nonflammable, and its vapors mixed with oxygen in proportions from 0.5 to 50 per cent (v/v) are not explosive.

FLUOTHANE does not decompose in contact with warm soda lime. When moisture is present, the vapor attacks aluminum, brass, and lead, but not copper. Rubber, some plastics, and similar materials are soluble in FLUOTHANE; such materials will deteriorate rapidly in contact with FLUOTHANE vapor or liquid. Stability of FLUOTHANE is maintained by the addition of 0.01 per cent thymol (w/w), up to 0.00025% ammonia (w/w), and storage is in amber colored bottles.

FLUOTHANE should not be kept indefinitely in vaporizer bottles not specifically designed for its use. Thymol does not volatilize along with FLUOTHANE, and therefore accumulates in the vaporizer, and may, in time, impart a yellow color to the remaining liquid or to wicks in vaporizers. The development of such discoloration may be used as an indicator that the vaporizer should be drained and cleaned, and the discolored FLUOTHANE (halothane, U.S.P.) discarded. Accumulation of thymol may be removed by washing with diethyl ether. After cleaning a wick or vaporizer, make certain all diethyl ether has been removed before reusing the equipment to avoid introducing ether into the system.

Actions. FLUOTHANE is an inhalation anesthetic. Induction and recovery are rapid and depth of anesthesia can be rapidly altered. FLUOTHANE progressively depresses respiration. There may be tachypnea with reduced tidal volume and alveolar ventilation. FLUOTHANE is not an irritant to the respiratory tract, and no increase in salivary or bronchial secretions ordinarily occurs. Pharyngeal and laryngeal reflexes are rapidly obtunded. It causes bronchodilation. Hypoxia, acidosis, or apnea may develop during deep anesthesia.

FLUOTHANE reduces the blood pressure, and frequently decreases the pulse rate. The greater the concentration of the drug, the more evident these changes become. Atropine may reverse the bradycardia. FLUOTHANE does not cause the release of catecholamines from adrenergic stores. FLUOTHANE also causes dilation of the vessels of the skin and skeletal muscles.

Cardiac arrhythmias may occur during FLUOTHANE anesthesia. These include nodal rhythm, AV dissociation, ventricular extrasystoles and asystole. FLUOTHANE sensitizes the myocardial conduction system to the action of epinephrine and norepinephrine, and the combination may cause serious cardiac arrhythmias. FLUOTHANE increases cerebral spinal fluid pressure. FLUOTHANE produces moderate muscular relaxation. Muscle relaxants are used as adjuncts in order to maintain lighter levels of anesthesia. FLUOTHANE augments the action of nondepolarizing relaxants and ganglionic blocking agents. FLUOTHANE is a potent uterine relaxant.

Indications. FLUOTHANE (halothane, U.S.P.) is indicated for the induction and maintenance of general anesthesia.

Contraindications. FLUOTHANE is not recommended for obstetrical anesthesia except when uterine relaxation is required.

Warnings. When previous exposure to FLUOTHANE was followed by unexplained jaundice, consideration should be given to the use of other agents.

FLUOTHANE should be used in vaporizers that permit a reasonable approximation of output, and preferably of the calibrated type. The vaporizer should be placed out of circuit in closed circuit rebreathing systems; otherwise overdosage is difficult to avoid. The patient should be closely observed for signs of overdosage, *i.e.*, depression of blood pressure, pulse rate, and ventilation, particularly during assisted or controlled ventilation.

Usage in Pregnancy. Safe use of FLUOTHANE has not been established with respect to possible adverse effects upon fetal development. Therefore, FLUOTHANE should not be used in women where pregnancy is possible and particularly during early pregnancy, unless, in the judgment of the physician, the potential benefits outweigh the unknown hazards to the fetus.

Precautions. The uterine relaxation obtained with FLUOTHANE, unless carefully controlled, may fail to respond to ergot derivatives and oxytocic posterior pituitary extract.

FLUOTHANE increases cerebrospinal fluid pressure. Therefore, in patients with markedly raised intracranial pressure, if FLUOTHANE is indicated, administration should be preceded by measures ordinarily used to reduce cerebrospinal fluid pressure. Ventilation should be carefully assessed, and it may be necessary to assist or control ventilation to insure adequate oxygenation and carbon dioxide removal.

Epinephrine or norepinephrine should be employed cautiously, if at all, during FLUOTHANE (halothane, U.S.P.) anesthesia since their simultaneous use may induce ventricular tachycardia or fibrillation.

Nondepolarizing relaxants and ganglionic blocking agents should be administered cautiously, since their actions are augmented by FLUOTHANE.

It has been reported that in genetically susceptible individuals, the use of general anesthetics and the muscle relaxant, succinylcholine, may trigger a syndrome known as malignant hyperthermic crisis. Monitoring temperature during surgery will aid in early recognition of this syndrome. Dantrolene sodium and supportive measures are generally indicated in the management of malignant hyperthermia.

Adverse Reactions. The following adverse reactions have been reported: mild, moderate and severe hepatic dysfunction (including hepatic necrosis), cardiac arrest, hypotension, respiratory arrest, cardiac arrhythmias, hyperpyrexia, shivering, nausea, and emesis.

Dosage and Administration. FLUOTHANE may be administered by the nonrebreathing technic, partial rebreathing, or closed technic. The induction dose varies from patient to patient. The maintenance dose varies from 0.5 per cent to 1.5 per cent.

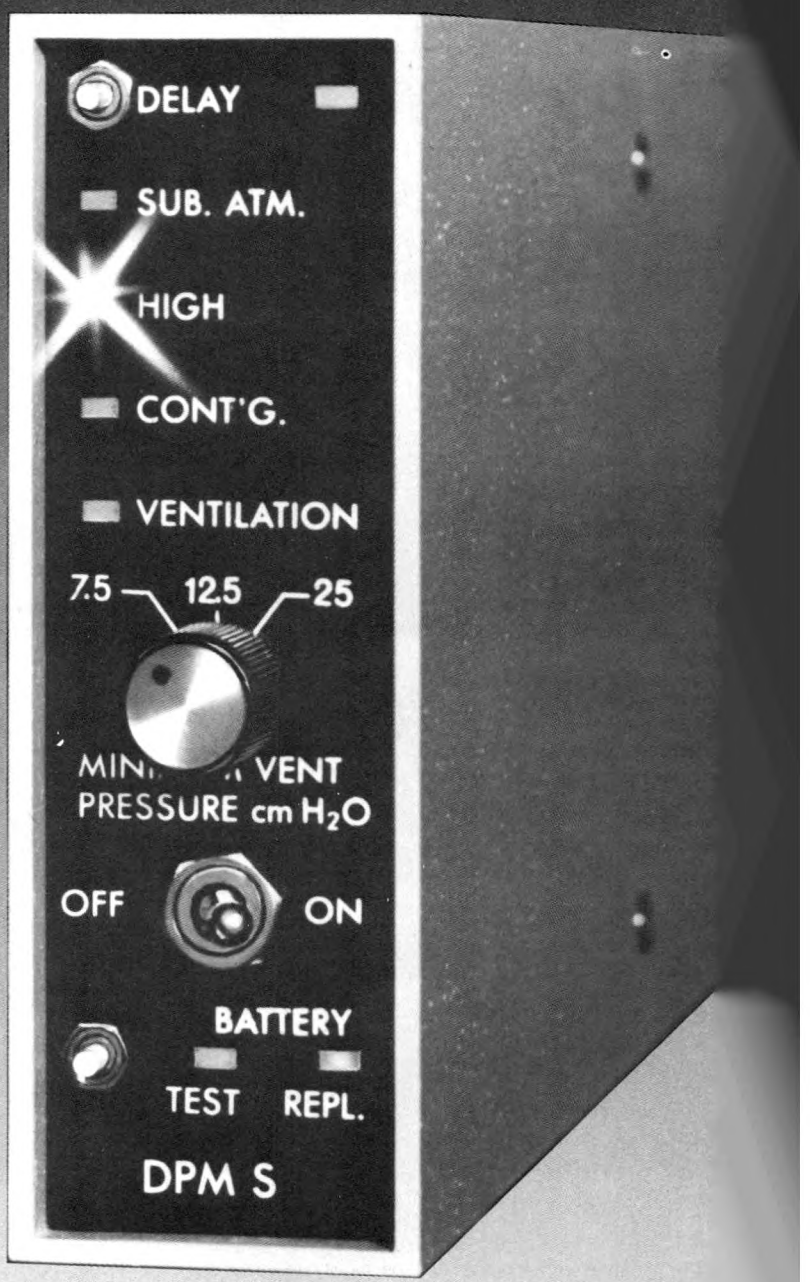
FLUOTHANE may be administered with either oxygen or a mixture of oxygen and nitrous oxide.

How Supplied. No. 3125—Unit packages of 125 ml and 250 ml of halothane, U.S.P., stabilized with 0.01% thymol (w/w), and up to 0.00025% ammonia (w/w). **7197/R82**

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  - a punctured ventilator bellows
  - an occluded tube
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with or without epinephrine 1:200,000

Please consult full prescribing information before prescribing. A summary follows:

Indications. Peripheral nerve block, infiltration, sympathetic block, caudal, or epidural block.

Contraindication. Marcaine is contraindicated in patients with known hypersensitivity to it.

Warnings. RESUSCITATIVE EQUIPMENT AND DRUGS SHOULD BE READILY AVAILABLE WHEN ANY LOCAL ANESTHETIC IS USED.

Usage in Pregnancy. The relevance to the human is not known. Safe use in pregnant women other than those in labor has not been established.

Until further clinical experience is gained, paracervical block with Marcaine is not recommended. Fetal bradycardia frequently follows paracervical block with some amide-type local anesthetics and may be associated with fetal acidosis. Added risk appears to be present in prematurity, toxemia of pregnancy, and fetal distress.

The obstetrician is warned that severe persistent hypertension may occur after administration of certain oxytocic drugs, if vasopressors have already been used during labor (e.g., in the local anesthetic solution or to correct hypotension).

Solutions containing a vasoconstrictor, particularly epinephrine or norepinephrine, should be used with extreme caution in patients receiving monoamine oxidase (MAO) inhibitors or antidepressants of the triptyline or imipramine types, because severe, prolonged hypertension may result.

Local anesthetics which contain preservatives, i.e., those supplied in multiple dose vials, should not be used for caudal or epidural anesthesia.

Until further experience is gained in children younger than 12 years, administration of Marcaine in this age group is not recommended.

Precautions. The safety and effectiveness of local anesthetics depend upon proper dosage, correct technique, adequate precautions, and readiness for emergencies.

The lowest dosage that gives effective anesthesia should be used in order to avoid high plasma levels and serious systemic side effects. Injection of repeated doses of Marcaine may cause significant increase in blood levels with each additional dose, due to accumulation of the drug or its metabolites or due to slow metabolic degradation. Tolerance varies with the status of the patient. Debilitated, elderly patients and acutely ill patients should be given reduced doses commensurate with age and physical condition.

Solutions containing a vasoconstrictor should be used cautiously in areas with limited blood supply, in the presence of diseases that may adversely affect the patient's cardiovascular system, or in patients with peripheral vascular disease.

Marcaine should be used cautiously in persons with known drug allergies or sensitivities, particularly to the amide-type local anesthetics.

Serious dose-related cardiac arrhythmias may occur if preparations containing a vasoconstrictor such as epinephrine are employed in patients during or following the administration of chloroform, halothane, cyclopropane, trichloroethylene, or other related agents. In deciding whether to use these products concurrently in the same patient, the combined action of both agents upon the myocardium, the concentration and volume of vasoconstrictor used, and the time since injection, when applicable, should be taken into account.

Caution is advised in administration of repeat doses of Marcaine to patients with severe liver disease.

Use in Ophthalmic Surgery. When Marcaine 0.75% is used for retrobulbar block, complete corneal anesthesia usually precedes onset of clinically acceptable external ocular muscle akinesia. Therefore, presence of akinesia rather than anesthesia alone should determine readiness of the patient for surgery.

Adverse Reactions. Reactions to Marcaine are characteristic of those associated with other amide-type local anesthetics. A major cause of adverse reactions to this group of drugs is excessive plasma levels, which may be due to overdosage, inadvertent intravascular injection, or slow metabolic degradation.

Excessive plasma levels of the amide-type local anesthetics cause systemic reactions involving the central nervous system and the cardiovascular system. The *central nervous system effects* are characterized by excitation or depression. The first manifestation may be nervousness, dizziness, blurred vision, or tremors, followed by drowsiness, convulsions, unconsciousness, and possibly respiratory arrest. Since excitement may be transient or absent, the first manifestation may be drowsiness, sometimes merging into unconsciousness and respiratory arrest. Other central nervous system effects may be nausea, vomiting, chills, constriction of the pupils, or tinnitus. The *cardiovascular manifestations* of excessive plasma levels may include depression of the myocardium, blood pressure changes (usually hypotension), and cardiac arrest. In obstetrics, cases of fetal bradycardia have occurred (see Warnings). *Allergic reactions*, which may be due to hypersensitivity, idiosyncrasy, or diminished tolerance, are characterized by cutaneous lesions (e.g., urticaria), edema, and other manifestations of allergy. Detection of sensitivity by skin testing is of doubtful value. Sensitivity to methylparaben preservatives added to multiple dose vials has been reported. Single dose vials without methylparaben are also available.

Reactions following epidural or caudal anesthesia also may include: high or total spinal block; urinary retention; fecal incontinence; loss of perineal sensation and sexual function; persistent analgesia, paresthesia, and paralysis of the lower extremities; headache and backache; and slowing of labor and increased incidence of forceps delivery.

Treatment of Reactions. Toxic effects of local anesthetics require symptomatic treatment; there is no specific cure. The physician should be prepared to maintain an airway and to support ventilation with oxygen and assisted or controlled respiration as required. Supportive treatment of the cardiovascular system includes intravenous fluids and, when appropriate, vasopressors (preferably those that stimulate the myocardium). Convulsions may be controlled with oxygen and intravenous administration, in small increments, of a barbiturate, as follows: preferably, an ultrashort-acting barbiturate such as thiopental or thiamylal; if this is not available, a short-acting barbiturate (e.g., secobarbital or pentobarbital) or diazepam. Intravenous barbiturates or anticonvulsant agents should only be administered by those familiar with their use.

Composition of Solutions.

Marcaine 0.25% — Each ml contains 2.5 mg bupivacaine with NaCl for isotonicity in water for injection.

Marcaine 0.5% — Each ml contains 5 mg bupivacaine with NaCl for isotonicity in water for injection.

Marcaine 0.75% — Each ml contains 7.5 mg bupivacaine with NaCl for isotonicity in water for injection.

In multiple dose vials, each ml also contains 1 mg methylparaben.

In epinephrine, each ml also contains 0.0091 mg epinephrine bitartrate, 0.5 mg sodium bisulfite, 0.001 ml monothioglycerol, 2 mg ascorbic acid, 0.0017 ml 60% sodium lactate, and 0.1 mg edetate calcium disodium.

References:

1. Scanlon JW: Obstetric anesthesia as a neonatal risk factor in normal labor and delivery. *Clinics in Perinatology* 1:465-482, 1974.
2. Scanlon JW, Ostheimer GW, Brown WU, et al: Neurobehavioral responses and drug concentrations in newborns after maternal epidural anesthesia with bupivacaine. *Anesthesiology* 45:400-405, 1976.
3. Ostheimer GW: Obstetrics and local anesthetics: Implications for the fetus and newborn. *Anesthesiology Review* 4:17-23, June 1977.

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ANESTH ANALG
1982;61:313-6

Renal and Biliary Elimination of Vecuronium (ORG NC 45) and Pancuronium in Rats

Robert A. Upton, PhD,* Trong-Lang Nguyen, PhD,† Ronald D. Miller, MD,‡ and Neal Castagnoli, Jr., PhD§

UPTON, R. A., NGUYEN, T.-L., MILLER, R. D., AND CASTAGNOLI, N., JR.: Renal and biliary elimination of vecuronium (ORG NC 45) and pancuronium in rats. Anesth Analg 1982;61:313-6.

The urinary excretion of ORG NC 45 (Vecuronium) and of pancuronium was studied in unanesthetized rats and the biliary excretion was studied in anesthetized rats. Urine and bile were analyzed for unchanged drug by a new and specific mass spectrometric assay. Pancuronium was eliminated primarily in the urine (85% ± 6% of the dose in 12 hours), but little ORG NC 45 appeared in the urine (3.5% ± 1.1% in 12 hours). Biliary excretion accounted for 46% ± 4% of the ORG NC 45 dose in 7 hours, but only 7.5% ± 5.3% of an injected dose of pancuronium appeared in the bile. Thus, it appears that ORG NC 45 (a monoquaternary ammonium compound) has a higher biliary clearance than pancuronium (a bisquaternary ammonium compound). The different biodisposition of these two compounds may be due to the greater lipophilicity and concomitant enhanced permeability into the hepatocyte of ORG NC 45. We conclude that in the rat elimination of pancuronium is primarily via the kidney whereas elimination of ORG NC 45 is dependent on nonrenal mechanisms.

Key Words: NEUROMUSCULAR RELAXANTS: Vecuronium, pancuronium.

ORG NC 45 (Vecuronium), a monoquaternary ammonium compound, is a new short acting non-depolarizing muscle relaxant. Durant, Houwertjes, and Crul (1) found that, unlike the case with the structurally related bisquaternary ammonium agent, pancuronium, the duration of neuromuscular blockade induced by ORG NC 45 was not significantly prolonged when the renal pedicles of cats were ligated. More recently, Fahey et al (2) found that the pharmacokinetics and duration of neuromuscular blockade of ORG NC 45, in contrast to those of pancuronium (3, 4) are not different in patients with and without renal failure. It therefore seems likely that ORG NC 45, unlike pancuronium, is not primarily dependent on renal excretion for its elimination in man. In an attempt to understand better the biodisposition characteristics of these compounds, we examined the elimination patterns of ORG NC 45 and pancuronium in rats. The results, which are consistent with, and therefore might explain, previously observed behavior of these compounds in humans (2-4), indicate that pancuronium and ORG NC 45 undergo different principal elimination pathways.

Method

Six male Sprague-Dawley rats, weighing 250 to 350 g each, were anesthetized with diethyl ether. Three rats were studied with ORG NC 45 and the remaining three were studied with pancuronium. A silicon catheter was inserted into the right jugular vein so that its distal tip rested in the vena cava and its exposed end emerged from the skin between the shoulder blades (5). Approximately 20 hours after they regained consciousness, these rats were placed unrestrained in a cage attached to a glass urine/feces separating device (Delmar, Maywood, IL), one animal to a cage. ORG NC 45 (N = 3) or pancuronium (N = 3) (150 μg/kg) in 0.5 ml of saline solution, was injected slowly through the jugular catheter. This was followed by

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This study was supported by the Anesthesia-Pharmacology Research Foundation, ORGanon, Inc., Oss (Holland) and National Institutes of Health grant GM-26043.
Received from the Departments of Pharmacy, Pharmaceutical Chemistry, Anesthesia, Pharmacology, and Chemistry, University of California, San Francisco, San Francisco, California. Accepted for publication November 24, 1981.

Reprint requests to Dr. Miller, Department of Anesthesia, S-436, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

0.25 ml of heparinized (10 units/ml) normal saline. Urine was collected under dichloromethane in a receptacle already containing the appropriate internal standard and the ion-pairing reagent as described below. The walls of the cage and separating device were rinsed frequently with a jet of water from a wash bottle to minimize spreading of the drug under conditions that might have been favorable for their decomposition. Rats were induced to urinate at the selected times (0, 1, 2, 3, 5, 8, and 12 hours after dosing) by compelling them to inhale ether fumes briefly beforehand (6). An intraperitoneal injection of normal saline (2 ml) was administered after each urine collection.

Bile was collected from six additional rats anesthetized with urethane (0.05 ml/kg) in a 25% solution administered intraperitoneally. Three were studied with ORG NC 45 and the remaining three with pancuronium. Anesthetized animals were placed on their backs, an abdominal incision was made, and the central section of the bile duct was exposed for a length of 1 to 2 cm. The duct was punctured with the needle end of a biliary cannula inserted into the duct toward the liver. The cannula was a 23-gauge hypodermic needle from which the hub had been replaced with a 75-mm length of silicon polymer (Silastic) tubing, 0.51 mm i.d., 0.94 mm o.d. The orientation of the cannula in the duct was adjusted to provide maximum flow and the bile was collected into a series of small receptacles, each wrapped in aluminum foil. Receptacles were changed at 0, 10, 20, 30, 40, 50, 60, 75, 90, 105, 120, 150, 180, 240, 300, 360, 420, 480, 540, 600, 660, and 720 minutes after administration of ORG NC 45 or pancuronium. Perfusion of the peritoneal cavity with normal saline (2 ml every 3 hours) permitted a more consistent bile flow. ORG NC 45 or pancuronium, 150 μg/kg, in approximately 0.5 ml of aqueous solution, was injected slowly into the right femoral vein exposed by removal of a small area of skin from the inside of the upper thigh.

ORG NC 45 and pancuronium were assayed in bile and urine by mass spectrometry (7). For each drug, the appropriate internal standard (the respective bis acetyl d_6 analog) in acetonitrile was added immediately upon collection of bile or urine samples. The drugs and internal standards were extracted from biologic samples by ion pair extraction into dichloromethane using iodide (KI) as the pairing ion. After evaporation of the solvent, the residue was dissolved in 1 ml of water and the aqueous phase washed with ether to remove neutral lipids. After re-extraction into dichloromethane, evaporation of the organic layer, and redissolution in acetonitrile, the samples were analyzed on a modified AEI MJ902 instrument by direct insertion, chemical ionization mass spectrometry using isobutane as the reagent gas. The analysis was carried out at a source temperature of 170°C, scanning from mass 553 to mass 540 at a rate of 38 minutes per decade. Ratios of the ion current at mass 543 ($MH^+ - 2CH_3I$ for pancuronium-d_0 and $MH^+ - CH_3I$ for ORG NC 45-d_0) to that at mass 549 ($MH^+ - 2CH_3I$ for pancuronium-d_6 and $MH^+ - CH_3I$ for ORG NC 45 d_6) were compared with standard curves constructed by analyzing spiked samples.

Statistical comparisons were made using Student's *t*-test.

Results

No rat receiving pancuronium excreted less than 78% of the unchanged drug in urine, whereas no rat receiving ORG NC 45 excreted more than 14% of the unchanged drug in urine (Table). Biliary excretion, in contrast, accounted for 46% ± 4% of the dose of ORG NC 45. As expected from the urine data, little pancuronium (3.5% ± 1.1% of dose) was excreted in bile. The differences between ORG NC 45 and pancuronium in the extent of their urinary excretion ($p <$

TABLE

Urinary and Biliary Excretion of an Intravenous Dose of ORG NC 45 or Pancuronium by Rats*

Rat	Urine (% of dose unchanged in urine after 12 hr)†	Bile (% of dose unchanged in bile after 7 hr)‡
ORG NC 45		
1	3.9	
2	13.6	
3	5.0	
	(7.5 ± 5.3)	
7		47.8
8		41.2
9		48.0
		(45.7 ± 3.9)
Pancuronium		
4	90.1	
5	85.7	
6	78.5	
	(84.8 ± 6.9)	
10		4.0
11		4.2
12		2.2
		(3.5 ± 1.1)

* Values in parentheses are means ± SD for three rats.

† Twenty-four hour urinary excretion of 16.0%, 5.6%, 90.7%, and 87.5% by rats 2, 3, 4, and 5, respectively.

‡ Ten-hour biliary excretion of 49.0%, 42.5%, 48.9%, and 2.5% by rats 7, 8, 9, and 12, respectively.

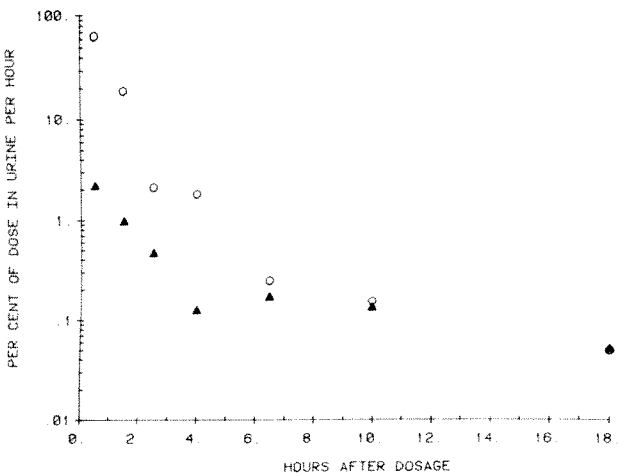


FIG 1. Excretion of ORG NC 45 (▲) and pancuronium (○) unchanged in urine in one rat.

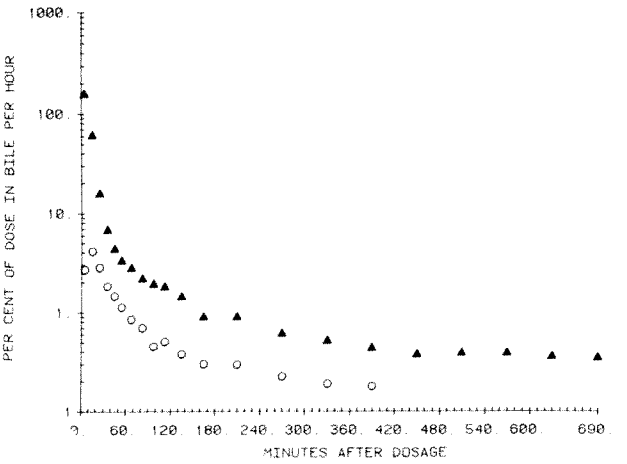


FIG 2. Excretion of ORG NC 45 (▲) and pancuronium (○) unchanged in bile in one rat.

0.001) and in the extent of their biliary excretion ($p < 0.001$) were statistically significant. Representative excretion rate plots for urinary and biliary excretion appear in Figs 1 and 2. In the case of both drugs, at the end of the sampling less than 0.3% of the dose was being excreted per hour in bile and less than 0.1% per hour in urine. Extending the urine collection period from 12 to 24 hours or the bile collection period from 7 to 10 hours did not result in significantly greater recovery of either drug (Table, footnote). In none of the rats was there any overt evidence of paralysis or inadequate breathing, although analysis of arterial blood gases was not performed.

Discussion

In the rat, pancuronium is eliminated almost exclusively in the urine whereas approximately 50% of an injected dose of ORG NC 45 is eliminated in the bile. Because our assay measures only unchanged ORG NC 45, we presume that the remaining 50% of this drug unaccounted for in either urine or bile has undergone metabolism. If this pattern approximates that of excretion in humans, then it might explain why little difference was found in the pharmacokinetics of ORG NC 45 in patients with and without normal renal function (2).

The greater plasma clearance reported for ORG NC 45 as compared with pancuronium in humans (2–4) suggests that the pattern of ORG NC 45 differs from that of pancuronium because of greater hepatic clearance rather than being merely due to a lesser renal clearance. The molecular structures of both drugs are identical except that the nitrogen atoms attached to both rings A and D of pancuronium are quaternized, whereas in ORG NC 45 only that attached to ring A is quaternized. The degree of polarity imposed upon the otherwise lipophilic steroid nucleus of both molecules should thus be considerably greater in the doubly quaternized and thus doubly charged pancuronium. It is possible in the case of ORG NC 45, which has only one fixed charge, that the lipophilic character of the steroid moiety dominates the partition characteristics of the molecule thereby facilitating entry into the hepatocyte. This would explain a concomitant greater biliary excretion and greater susceptibility to hepatic metabolism of ORG NC 45 than of pancuronium. Similar polarity considerations might also predict greater reabsorption of ORG NC 45 from the renal tubules allowing potentially less renal clearance of ORG NC 45 than of pancuronium.

As the data obtained show little variability, those from ORG NC 45 were found to be different from those of pancuronium at a high level of significance even though only three animals were studied in each group. We therefore conclude that elimination of ORG NC 45 appears to be relatively independent of renal excretion, and for this reason, this drug may be the preferred non-depolarizing muscle relaxant in patients with impaired renal function.

REFERENCES

1. Durant NN, Houwertjes MC, Crul JF. Comparison of neuromuscular blocking properties of ORG NC 45 and pancuronium in the rat, cat and rhesus monkey. Br J Anaesth 1980;52:723–8.
2. Fahey MR, Morris RB, Miller RD, Nguyen T-L, Upton RA. Pharmacokinetics of ORG NC 45 (Norcuron™) in patients with and without renal failure. Br J Anaesth 1981;53:1049–53.
3. McLeod K, Watson MJ, Rawlins MD. Pharmacokinetics of pancuronium in patients with normal and impaired renal functions. Br J Anaesth 1976;48:341–5.

4. Somogyi AA, Shanks CA, Triggs EJ. The effect of renal failure on the disposition and neuromuscular blocking action of pancuronium bromide. Eur J Clin Pharmacol 1977;12:23–9.
5. Upton RA. Simple and reliable method for serial sampling of blood from rats. J Pharm Sci 1975;64:112–4.
6. Nelson E, Hanano M, Levy G. Comparative pharmacokinetics of salicylate elimination in man and rats. J Pharmacol Exp Ther 1966;153:159–66.
7. Nguyen T-L, Gruenke LD, Upton RA, Castagnoli N, Miller RD. Quantitative analysis in biological fluids of the quaternary ammonium salts, pancuronium and norcuron (ORG NC 45), by direct insertion CIMS. Biomed Mass Spec (in press 1982).

Lack of Effect of Bed Rest on Incidence of Lumbar Puncture Headache

The influence of bed rest on postlumbar puncture headache was examined in 100 patients in whom lumbar puncture (LP) was performed for diagnostic reasons. Fifty patients were mobilized immediately following the procedure and 50 remained in bed for 24 hours before resuming their normal activities. All LPs were performed with an 18-gauge needle. The two groups of patients were comparable in age, sex, and psychological profile. Of the ambulant patients, 19 (38%) complained of headache, compared with 18 (36%) patients in the bed rest group (p = NS). These data suggest that enforced bed rest following lumbar puncture is not justified. *(Carbaat PAT, van Crevel H. Lumbar puncture headache: controlled study on the preventive effect of 24 hours' bed rest. Lancet 1981;2:1133–5)*

Effect of Heparin Bonding on Thrombogenicity of Pulmonary Artery Catheters

Twenty male patients undergoing elective coronary artery bypass surgery were randomly assigned to receive one of two types of No. 7 French thermodilution pulmonary artery catheters. The 10 heparin-bonded catheters (Safe-T-Coat, USCI Cardiology and Radiology Products) and the 10 non-heparin-bonded catheters (Swan-Ganz 93A-131-7F, Edwards Laboratories) were placed in similar fashion. Immediately before surgery, catheters filled and continuously flushed with heparinized saline (1000 units of heparin in 500 ml of normal saline) were percutaneously inserted with a No. 8 French introducer into the internal jugular vein and were flow directed to achieve the most proximal, nonpermanent "wedge" position possible in the pulmonary artery. After the institution of total cardiopulmonary bypass, an atriotomy was performed, which allowed temporary displacement and direct examination of the catheters from the tip to the level of the right atrium (approximately 30 cm). No thrombi were observed on any of the heparin-bonded catheters; in contrast, thrombi were found on the surface of all non-heparin-bonded catheters. These results suggest that the use of heparin-bonded catheters may decrease the incidence of complications related to thrombus formation at least over the short term. No data are provided on the antithrombogenic properties of heparin-bonded catheters when used for extended periods. However, data in animals indicate that heparin-bonded pulmonary artery catheters remain thrombus-free for at least several days after placement. Therefore, the antithrombogenic properties provided by heparin bonding should extend through the perioperative period as well as encompass the time required for cardiac catheterization procedures. *(Hoar PF, Wilson RM, Mangano DT, Avery GJ II, Szarnicki RJ, Hill JD: Heparin bonding reduces thrombogenicity of pulmonary-artery catheters. N Engl J Med 1981;305:993–5)*

ANESTH ANALG
1982;61:317-22

Acute Cardiovascular Toxicity of Intravenous Amide Local Anesthetics in Anesthetized Ventilated Dogs

Philip Liu, MD,* Hal S. Feldman, BSc,† Brian M. Covino, AB,‡ Robert Giasi, MD,§ and Benjamin G. Covino, PhD, MD‖

LIU, P., FELDMAN, H. S., COVINO, B. M., GIASI, R., AND COVINO, B. G.: Acute cardiovascular toxicity of intravenous amide local anesthetics in anesthetized ventilated dogs. Anesth Analg 1982;61:317–22.

The acute intravenous cardiovascular toxicity of five amide local anesthetic agents was studied in intact, ventilated dogs anesthetized with pentobarbital. Minimal changes in various cardiovascular functions were seen at doses of 0.3 to 3.0 mg/kg. At 10 mg/kg profound hypotension accompanied by significant decreases in cardiac output and stroke volume were observed with etidocaine and bupivacaine. At this dose lidocaine, mepivacaine, and prilocaine produced moderate signs of cardiovascular depression. Myocardial depression appeared to be primarily responsible for the profound hypotension, as minimal changes in peripheral vascular resistance occurred except as a terminal event. Pulmonary vascular resistance tended to increase before myocardial depression, suggesting a pulmonary vasoconstrictor action of the anesthetics. The cumulative lethal dose varied from appproximately 80 mg/kg for lidocaine and mepivacaine to 40 mg/kg for etidocaine and 20 mg/kg for bupivacaine. The acute cardiovascular toxicity of these agents is proportional to their comparative in vivo anesthetic potency which indicates little difference in therapeutic ratio between the various amide local anesthetics.

Key Words: ANESTHETICS, Local: amide; TOXICITY: local anesthetics.

FEW DETAILED studies are available concerning the comparative cardiovascular toxicity of the various local anesthetic drugs currently in clinical use. Stewart et al (1) evaluated the effects of different agents on the cardiac output of dogs, but mepivacaine, prilocaine, bupivacaine, and etidocaine were not available at the time of that investigation. The severe cardiac toxicity of the new longer-acting local anesthetic agents reported recently (2, 3) suggests that additional investigations of the cardiovascular effects of these newer agents compared with the older drugs such as lidocaine are indicated. Although these reports (2, 3) maintained that hypoxia and/or acidosis were not factors in their cases, Moore et al (4) have recently demonstrated the rapid onset of hypoxia and acidosis associated with bupivacaine toxicity. To preclude the possible complicating factors of convulsive activity, hypoxia, and acidosis, we used anesthetized, ventilated dogs in the current study to investigate the comparative cardiovascular effects of all presently available amide local anesthetics.

Methods and Materials

Twenty-five adult mongrel dogs of either sex, weighing 16.8 ± 1.3 kg each, were anesthetized with 30 mg/kg of sodium pentobarbital intravenously. Each drug group consisted of five randomly selected animals. Anesthesia was maintained with supplemental doses of intravenous pentobarbital as required. All animals were placed in the supine position on a surgical table. Body temperature was maintained with a heating pad placed under the animal. Rectal temperature was monitored via a rectal probe and a Yellow Springs-SC thermometer. A tracheal tube with inflatable cuff of proper size was used for tracheal intubation. The animals were ventilated using a Harvard animal respirator with oxygen-enriched room

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Supported in part by a grant from A. B. Astra, Sweden.
Received from the Departments of Anesthesia, Brigham and Women's Hospital and Harvard Medical School, Boston, and Department of Anesthesiology, University of Massachusetts Medical Center, Worcester, Massachusetts. Accepted for publication December 3, 1981.

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air. Arterial pH, P_{CO_2}, and P_{O_2} were maintained at physiologic levels. Polyethylene catheters were surgically implanted in a cephalic vein, the abdominal aorta, a femoral artery, and in the inferior vena cava via a femoral vein. The cephalic catheter was used for drug administration, and the femoral arterial catheter was attached to a Statham blood pressure transducer for direct recording of arterial blood pressure.

A #7 French thermodilution cardiac output catheter of custom construction was used. This catheter had the proximal lumen located at 15 cm from the tip to allow accurate measurements of cardiac output in dogs. The catheter was introduced via the right external jugular vein and advanced using pressure monitoring until the distal tip was located in the pulmonary artery. Cardiac output was measured using room temperature injectate and calculated by a Lexington cardiac ouput calculator.

Arterial blood pressure, pulmonary arterial pressure, and lead II electrocardiogram were recorded on a Grass model 79B polygraph. Strip chart records were taken at control, end injection, and 15 and 29 minutes after injection. Heart rate; systolic, diastolic, and mean systemic and pulmonary arterial blood pressures; cardiac output; stroke volume; cardiac index; and systemic and pulmonary vascular resistance were directly measured or calculated.

Commercially available, preservative-free local anesthetic solutions were used: lidocaine, 2%; bupivacaine, 0.5%; prilocaine, 3%; mepivacaine, 2%; and etidocaine, 1%. Administration of test solution was begun after a 45- to 60-minute equilibration period. Each animal received increasing serial doses of 0.3, 1.0, 3.0, and 10.0 mg/kg of the various local anesthetics at 30-minute intervals. After the administration of the 10-mg/kg dose of each agent the dosing schedule varied at 30-minute intervals as follows: 20, 30, and 40 mg/kg of lidocaine and mepivacaine; 20 and 30 mg/kg of etidocaine; 30 mg/kg of prilocaine; and 15 mg/kg of bupivacaine. The single and cummulative doses that caused irreversible cardiovascular toxicity of each agent except prilocaine were determined. No attempt to resuscitate or otherwise revive the animals was made. The data were analyzed statistically using paired data Student's *t*-test to compare control values with values following injection, and group mean Student's *t*-test was used to compare the effect of the different local anesthetic agents.

Results

Heart Rate, Cardiac Output, Stroke Volume, and Diastolic Pulmonary Artery Pressure

No significant changes in heart rate were observed with any of the anesthetics at doses varying from 0.3 to 3.0 mg/kg (Fig 1). At 10 mg/kg, no significant changes were produced by mepivacaine, prilocaine, lidocaine, or etidocaine. At this dose four of the dogs given bupivacaine showed progressive sinus bradycardia which ultimately resulted in death. At 30 mg/kg all remaining drugs caused decreases in cardiac rate of 60% to 100% ($p < 0.01$).

At doses of 0.3 and 1.0 mg/kg, there was a slight but statistically insignificant increase in cardiac output with all of the anesthetics agents except etidocaine which was associated with an insignificant decrease in cardiac ouput (Fig 2). At 3 mg/kg, all agents

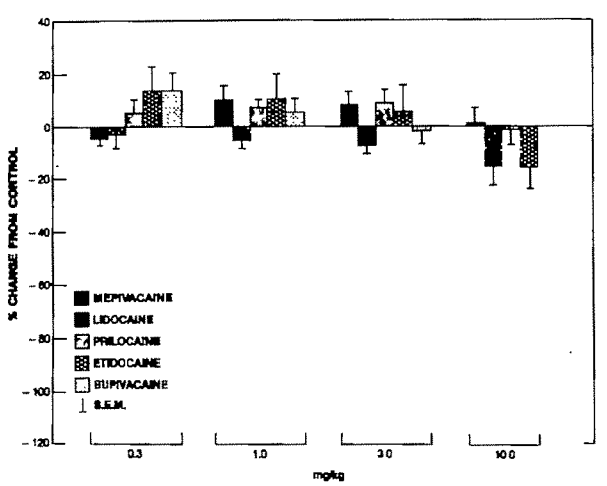


FIG 1. Percent change in heart rate following various doses of amide local anesthetic agents. No data are presented for 10 mg/kg of bupivacaine as four of the animals died at this dose.

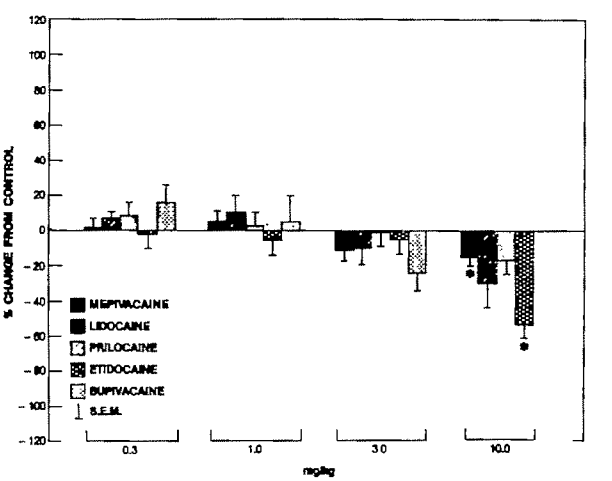


FIG 2. Percent change in cardiac output following various doses of amide local anesthetic agents. No data are presented for 10 mg/kg of bupivacaine as four of the animals died at this dose (*$p < 0.01$).

produced a statistically insignificant depression of cardiac output. Significant decreases in cardiac output were seen when 10 mg/kg of mepivacaine and etidocaine were administered ($p < 0.01$). As indicated above, bupivacaine proved to be lethal in four of the five dogs at 10 mg/kg. At this dose, there was a statistically significant difference between etidocaine and the other three amide local anesthetics ($p < 0.01$). At 30 mg/kg, 90% to 100% depressions of cardiac output occurred with all of the anesthetics agents ($p < 0.01$).

There were only minor changes in stroke volume following doses of 0.3 to 1.0 mg/kg (Fig 3). Only etidocaine was associated with a consistent but insignificant decrease in stroke volume at these doses. At 3 mg/kg, a modest decrease in stroke volume occurred with all of the anesthetic agents. By 10 mg/kg, significant depression of stroke volume was evident with all agents except lidocaine ($p < 0.01$). The decrease in stroke volume produced by etidocaine was significantly greater than that caused by the other three amide agents ($p < 0.01$). The 30-mg/kg dose resulted in an 80% to 100% decrease in stroke volume with all remaining agents.

At no time during the protocol were increases in pulmonary diastolic pressure recorded. When there were decreases in cardiac ouput and stroke volume this was reflected by a decrease in pulmonary diastolic pressure.

Systemic Vascular Effects

Insignificant changes in mean arterial blood presure (MABP) were observed as the doses of the anesthetics were increased from 0.3 to 1.0 mg/kg (Fig 4). At 3 mg/kg all agents produced a moderate decrease in MABP. However, only prilocaine, etidocaine, and bupivacaine caused a statistically significant degree of hypotension ($p < 0.01$). Etidocaine decreased MABP by 19% ± 4%; the other four agents decreased MABP by 2% to 12%. The differences between agents were not statistically significant. At a dose of 10 mg/kg, all drugs caused a marked and significant hypotensive effect ($p < 0.01$). The greatest decrease in MABP occurred following administration of bupivacaine (80% deaths) and etidocaine (67% ± 8%). Prilocaine, lidocaine, and mepivacaine produced a decrease in MABP of 14% to 27%. The decrease in MABP following administration of etidocaine was significantly greater than that seen with the other three drugs ($p < 0.01$). At 30 mg/kg, severe hypotension of 80% to 100% occurred with all remaining agents.

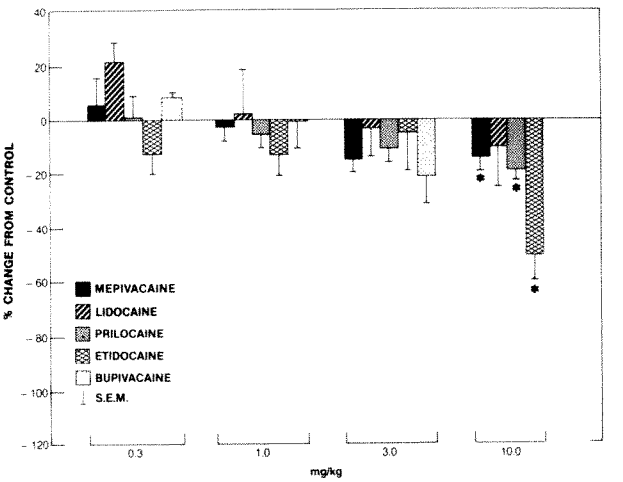


FIG 3. Percent change in stroke volume following various doses of amide local anesthetic agents. No data are presented for 10 mg/kg of bupivacaine as four of the animals died at this dose (*$p < 0.01$).

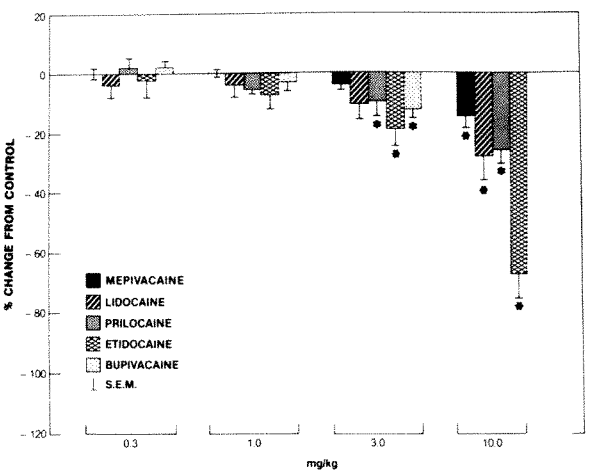


FIG 4. Percent change in mean arterial blood pressure following various doses of amide local anesthetic agents. No data are presented for 10 mg/kg of bupivacaine as four of the animals died at this dose (*$p < 0.01$).

No consistent alteration in total peripheral vascular resistance (TPR) was observed as doses of local anesthetics agents was increased from 0.3 to 10 mg/kg (Fig 5). Changes in TPR produced by lidocaine, etidocaine, mepivacaine, and prilocaine at these doses were not statistically significant. Likewise, bupivacaine caused no significant change in TPR at doses less than 10 mg/kg.

Pulmonary Vascular Effects

All five agents increased mean pulmonary arterial pressure (PAP) at doses of 0.3 to 3.0 mg/kg (Fig 6). However, only bupivacaine caused a statistically sig-

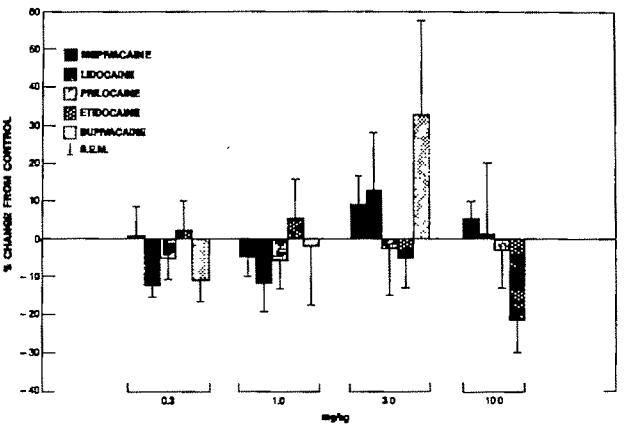


FIG 5. Percent change in total peripheral resistance following various doses of amide local anesthetic agents. No data are presented for 10 mg/kg of bupivacaine as four of the animals died at this dose.

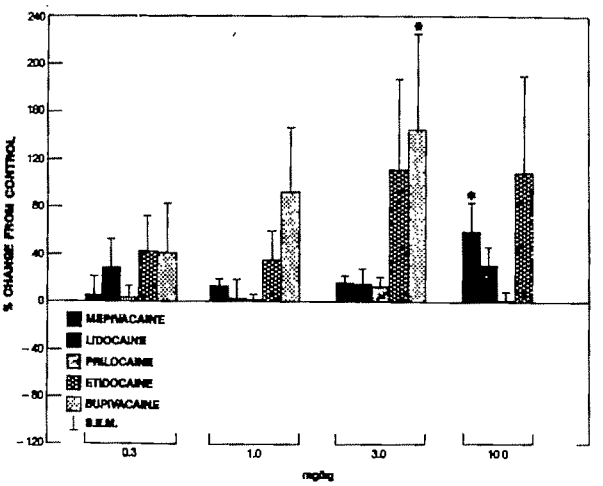


FIG 6. Percent change in mean pulmonary arterial blood pressure following various doses of amide local anesthetic agents. No data are presented for 10 mg/kg of bupivacaine as four of the animals died at this dose ($*p < 0.01$).

nificant increase in PAP at 3 mg/kg ($p < 0.01$). The administration of 10 mg/kg of mepivacaine, lidocaine, and etidocaine resulted in increases of 61%, 33%, and 109%, respectively. At this dose, prilocaine produced no change in PAP. However, only the changes produced by mepivacaine were sufficiently consistent to achieve statistical significance at the 0.01 level. At the 30 mg/kg dose, all remaining anesthetics caused profound decreases in PAP.

The changes in pulmonary vascular resistance illustrated in Fig 7 generally reflect a progressive increase as the dose of drug increased from 0.3 to 10 mg/kg. The increase in pulmonary vascular resistance was most pronounced with bupivacaine at 3.0 mg/kg (240% increase from control levels) and at the 10 mg/kg dose with etidocaine (743% increase in pulmonary

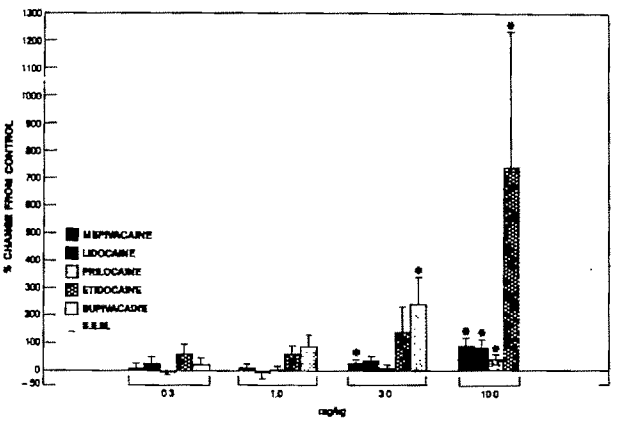


FIG 7. Percent change in pulmonary vascular resistance following various doses of amide local anesthetic agents. No data are presented for 10 mg/kg of bupivacaine as four of the animals died at this dose ($*p < 0.01$).

TABLE

Lethal Doses in Anesthetized Ventilated Dogs of Various Local Anesthetics

Drug*	Single dose causing death	Cumulative dose causing death
	mg/kg	
Bupivacaine (Marcaine)	11 ± 1.0	20.4 ± 2.4
Etidocaine (Duranest)	22 ± 2.0	40.4 ± 6.0
Prilocaine (Citanest)	30 ± 0	—
Lidocaine (Xylocaine)	28 ± 1.22	76.2 ± 15.1
Mepivacaine (Carbocaine)	33.3 ± 2.1	80.4 ± 9.7

* Values are means ± SE; n = 5 throughout. Tradenames are shown in parentheses.

vascular resistance). The 10-mg/kg dose produced increases in pulmonary vascular resistance of 96%, 84%, and 44% following mepivacaine, lidocaine, and prilocaine, respectively.

Lethal Dose

The single and cumulative lethal doses of the various drugs are presented in the Table. The average individual dose to cause death in all animals varied from 11 ± 1.0 mg/kg for bupivacaine to 33.3 ± 2.1 mg/kg for mepivacaine. With regard to cumulative lethal doses, lidocaine and mepivacaine caused irreversible cardiovascular depression and death at doses of approximately 80 mg/kg. The cumulative lethal dose of etidocaine was 40.4 ± 6.0 mg/kg, whereas bupivacaine caused death at an accumulated dose of 20.4 ± 2.4 mg/kg. The cumulative lethal dose of prilocaine was not determined due to differences in dosing schedule. Death occurred following progressive hypotension, sinus bradycardia, and ultimately cardiac asystole. There were no increases in pulmonary diastolic pressure before the hypotension and

bradycardia. No evidence of cardiac arrhythmias was seen before terminal cardiac arrest. Electrical cardiac activity persisted after the blood presure and cardiac output had decreased to zero, suggesting that pump failure was the primary cause of death.

Discussion

The present study demonstrates that all amide local anesthetic agents can produce profound cardiovascular depression which may lead to death. The sequence of events that occurred as the dose progressively increased was similar for all the agents. Minimal cardiac or peripheral vascular effects were noted at doses less than 3 mg/kg. Small increases in cardiac output were seen with all drugs except etidocaine at doses of 0.3 and 1.0 mg/kg. Similar reports of a positive inotropic action of lidocaine were reported by Kao and Jalar (5) who suggested that this phenomenon was secondary to a central nervous system stimulatory effect of lidocaine. At 3 mg/kg, decreases in mean cardiac output and stroke volume occurred with all agents, but the decrease was most prounced following the administration of bupivacaine. At 10 mg/kg considerable depression of all cardiovascular functions occurred with all of the drugs. However, bupivacaine and etidocaine were more cardiodepressant at this dose than were prilocaine, lidocaine, and mepivacaine. In fact, four of the dogs given bupivacaine died at this dose. The primary toxic effect appears to involve the myocardium rather than the peripheral vasculature. Changes in total peripheral vascular resistance were inconsistent, indicating that the profound hypotension at doses of 10 mg/kg and greater were related primarily to a negative inotropic action of the anesthetics. This finding is consistent with the observations of Craft et al (6) who reported decreases in TPR with a 10-mg dose of bupivacaine and an increase in TPR with a 40-mg dose of bupivacaine in pregnant ewes.

All dogs received basal pentobarbital anesthesia in these studies. Barbiturate anesthesia is known to be a cardiovascular depressant. Therefore, if the pentobarbital anesthetic had any effect on results of these studies, its contribution would probably be to enhance cardiovascular depression. There is little reason to believe that pentobarbital should alter the cardiovascular effects of the various local anesthetics differently.

Interestingly, pulmonary vascular resistance tended to increase as the dose of local anesthetic drug increased. This effect was most pronounced with etidocaine and bupivacaine. The three agents of intermediate anesthetic potency also demonstrated increases in PAP and pulmonary vascular resistance but of a lesser magnitude. The increase in pulmonary vascular resistance occurred before the profound decrease in cardiac output, which tends to rule out the possibility that the pulmonary hypertension was secondary to a decrease in left ventricular contractile force. The results suggest that local anesthetics may exert a direct constrictor effect on the pulmonary vasculature, an observation that has not been reported previously to our knowledge.

The comparative cardiovascular toxicity of the local anesthetics used in this study does not support the suggestion by Albright (2) that bupivacaine and etidocaine are selectively more cardiodepressant than are agents such as lidocaine. The cumulative lethal dose of bupivacaine was 25% of that of lidocaine and mepivacaine. The cumulative lethal dose of etidocaine was 50% of that of the less potent local anesthetics. The results agree with the relative subcutaneous and intraperitoneal acute lethal doses of lidocaine, bupivacaine, and etidocaine reported in mice (7, 8). The relative cardiovascular toxicity of the amide local anesthetics is proportional to that in vivo local anesthetic potencies. Data from clinical studies indicate that local anesthetic potencies of bupivacaine and etidocaine in man are 4 and 2 times greater, respectively, than that of lidocaine (9). Therefore, little difference in therapeutic ratio or margin of safety appears to exist between the various amide local anesthetic drugs. The possibility of hypoxia and acidosis as predisposing factors for the severe cardiac depression reported with bupivacaine and etidocaine in several patients cannot be ruled out. As recently shown by Moore et al (4), severe hypoxia and acidosis can occur within minutes in patients accidentally having intravascular injection of toxic amounts of bupivacaine.

The recent report of cardiac arrhythmias following intravenous fusion of bupivacaine in cats (10) and the development of ventricular fibrillation in the one etidocaine-treated patient reported by Prentiss (3) were not substantiated in this study. No reports of cardiac arrhythmias appeared in the previous toxicity studies conducted in sheep, dogs, or monkeys with bupivacaine and etidocaine (11–13). The appearance of cardiac arrhythmias in cats following bupivacaine infusion may represent a true species differences (10).

In general, the results of this study indicate that the cardiovascular system is relatively resistant to the toxic effects of local anesthetic drugs. This study

supports the observations in sheep (11) that the cardiovascular system is far more resistant to the toxic effects of lidocaine than is the central nervous system. In this study, doses of 10 mg/kg of bupivacaine and etidocaine were required to produce profound cardiovascular depression. This would be the equivalent of a 70-kg patient receiving an intravenous bolus injection of 700 mg of these agents, a situation which should never be allowed to occur clinically.

ACKNOWLEDGMENTS

The authors would like to express their gratitude to Deborah Bradstreet, Cheryl Latka, Steven Crespo, and Catherine Waud for their expert technical assistance.

REFERENCES

1. Stewart DM, Rogers WP, Mahaffey JE, et al. Effect of local anesthetics on the cardiovascular system of the dog. Anesthesiology 1963;620–4.
2. Albright GA. Cardiac arrest following regional anesthesia with etidocaine or bupivacaine. Anesthesiology 1979;51:285–7.
3. Prentiss JE. Cardiac arrest following caudal anesthesia. Anesthesiologyy 1979;50:51–3.
4. Moore DC, Crawford RD, Scurlock JE. Severe hypoxia and acidosis following local anesthetic-induced convulsions. Anesthesiology 1980;53:259–60.
5. Kao F, Jalar U. The central action of lignocaine and its effect on cardiac output. Br J Pharmacol 1959;14:522–30.
6. Craft JB Jr, Co EG, Yonekura ML, et al. Intravenous injection of bupivacaine in the pregnant ewe. Anesthesiology 1979;51: S309.
7. Adams HJ, Kronberg GH, Takman BH. Local anesthetic activity and acute toxicity of (±)-2-(N-ethylpropylamino)-2',6'-butyroxylidide, a new long-acting agent. J Pharm Sci 1972;61: 1829–31.
8. de Jong RH, Bonin JD. Deaths from local anesthetic-induced convulsions in mice. Anesth Analg 1980;59:401–5.
9. Covino BG. Pharmacology of newer local anesthetic agents. Int Anesthesiol Clin 1978;16:1–22.
10. de Jong RH, DeRosa RA, Bonin JD, et al. Cerebral and circulatory effects of high-dose bupivacaine and etidocaine. Anesthesiology 1980;53:S224.
11. Morishima HO, Pedersen H, Sakuma K, et al. Toxicity of lidocaine and etidocaine in the fetal, newborn and adult sheep. Anesthesiology 1981;55:57–61.
12. Eicholzer AW, Feldman HS. Acute toxicity of etidocaine following various routes of administration in the dog. Toxicol Appl Pharmacol 1976;37:13–21.
13. Munson ES, Tucker WK, Ausinsch B, et al. Etidocaine, bupivacaine and lidocaine seizure thresholds in monkeys. Anesthesiology 1975;42:471–8.

Diagnosis of Acute Anaphylactoid Reactions

Patients with a presumptive diagnosis of an acute anaphylactoid reaction to anesthetic agents were investigated by intradermal testing, patch prick testing, sequential complement measurement, passive transfer testing, and challenge. Of 165 patients, 142 were investigated following life-threatening reactions during anesthesia, 14 patients were tested after reactions confined to the skin or reactions that resolved without treatment, and nine patients presented with a history of "allergy to anesthetics," without further clinical details. The most valuable information was provided by intradermal testing, and a diagnosis could be made in 150 of the 165 patients. When anaphylactoid reactions to anesthetic drugs occur, intradermal testing 1 month after the reaction and sequential complement measurements in the immediate postreaction period will enable the diagnosis to be established in the majority of cases. Intradermal testing is of no value for trivial reactions or reactions to colloid solutions or contrast media. *(Fisher MMcD. The diagnosis of acute anaphylactoid reactions to anaesthetic drugs. Anaesth Intensive Care 1981;9:235–41)*

ANESTH ANALG
1982;61:323-32

Oxygenation during High-Frequency Ventilation Compared with Conventional Mechanical Ventilation in Two Models of Lung Injury

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KOLTON, M., CATTRAN, C. B., KENT, G., VOLGYESI, G., FROESE, A. B., AND BRYAN, A. C.: Oxygenation during high-frequency ventilation compared with conventional mechanical ventilation in two models of lung injury. Anesth Analg 1982;61:323-32.

Oxygenation and mean lung volume were investigated during high frequency oscillation (HFO) and conventional mechanical ventilation (CMV) in two models of lung disease and related to the lung mechanics of the lesions. Oleic acid (n = 10) or lung lavage (n = 12) pulmonary injury was induced in a series of rabbits. Each animal was alternately ventilated with HFO (15 Hz sinusoidal wave form) and CMV (flow generator I:E, 1:2; f, 30 breaths/min; V_T, 10 to 15 ml/kg) at matched mean airway pressure. Pa_{O_2} was measured 5 minutes after onset of ventilation. In the lung lavage model Pa_{O_2} was significantly greater during HFO than CMV (Pa_{O_2} 228 ± 116 torr vs 71 ± 42 torr) provided that mean airway pressure was greater than the distinct opening pressure characteristic of this lesion. In the oleic acid model oxygenation was again superior during HFO (Pa_{O_2} 269 ± 116 torr vs 110 ± 83 torr), but only if HFO was preceded by a sustained inflation. Plethysmography in a subset of six rabbits from each group revealed that the improvements in oxygenation were associated with significantly higher mean lung volumes during HFO than CMV (58 ± 30 ml vs 29 ± 14 ml lung lavage model, 45 ± 15 ml vs 30.9 ± 13 ml on the oleic acid model). The importance of a sustained inflation in rapidly optimizing gas exchange during HFO but not CMV was demonstrated. A sustained inflation resulted in immediate and sustained increases in Pa_{O_2} (from 134 ± 102 torr to 274 ± 124 torr in the oleic acid model; from 115 ± 105 torr to 291 ± 143 torr in the lung lavage model) and mean lung volume (41.8 ± 11 to 53.8 ± 9.7 ml in the oleic acid model, 30.9 ± 7.7 ml to 42.8 ± 5 ml in the lung lavage model). It is suggested that in these two particular models of lung disease, HFO, when combined with a sustained inflation (to provide opening forces), can more fully exploit the pressure volume hysteresis of unstable lung units than CMV, thereby resulting in the larger mean lung volumes and better oxygenation observed during HFO.

Key Words: VENTILATION: high-frequency; LUNG: respiratory distress model.

THE TREATMENT for the hypoxemia of both adult and infant respiratory distress syndrome is highly dependent on the recruitment and maintenance of lung volume (1, 2). Attempts to maximize this gas exchanging volume have focused on both phases of the ventilatory cycle with the use of a positive distending pressure at end expiration (PEEP), or increasing time integrated volume during inspiration (reversed I:E ratio).

Several investigators (1-4) have concluded that, for all practical purposes, oxygenation is tightly linked to the mean distending pressure applied to the lung, rather than to any specific detail of the ventilatory pattern (tidal volume, I:E ratio, PEEP, inspiratory hold). Inherent in all these previous studies has been the assumption that, for any given mean airway pressure (MAP), comparable mean lung volumes (MLV) were being achieved (1, 2). However, it is well recognized that lung volume is not uniquely related to distending pressure. The static pressure-volume (PV) curve demonstrates marked hysteresis, with a large difference in volume for the same pressure on the

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Received from the Departments of Respiratory Physiology, Surgical Research, and Anesthesia, Research Institute, The Hospital for Sick Children, Toronto, Ontario, Canada. Accepted for publication December 17, 1981.

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inflation and deflation limbs. Hoppin and Hildebrandt (5) have recently reviewed the volume and time dependence of these pressure/volume relationships. Clinically, these PV relationships have been difficult to exploit. Perhaps the best known failure was the introduction of intermittent "sighs" during conventional mechanical ventilation (CMV) in an attempt to reopen atelectatic areas of the lung. In doing this, one would theoretically move onto the more compliant deflation limb of the lung PV curves. But the effect proved to be clinically of little value (6).

In this paper we show that with HFO one can take advantage of the hysteresis of the lung PV curve and at the same MAP achieve a greater lung volume and higher Pa_{O_2} than on CMV in two different models of lung disease.

Methods

A total of 22 New Zealand White rabbits, each 2 to 4 kg in weight, were studied. The rabbits were premedicated with acepromazine, 15 mg, subcutaneously before induction of anesthesia with ketamine, 2 mg/kg IV, anesthesia and paralysis subsequently being maintained with intermittent pentobarbital and pancuronium. Tracheostomy was performed and the trachea cannulated with a 3.5- to 4-mm i.d. endotracheal tube. An arterial line was inserted through the femoral artery. Dextrose (5%) in 0.2% normal saline was infused at a rate of 3 ml/hr.

An esophageal temperature probe was inserted and body temperature maintained by use of an overhead radiant heater. The arterial line was connected to a Hewlett-Packard pressure transducer model 1280 and mean arterial pressure was recorded.

Ventilation

Conventional mechanical ventilation (CMV) was provided by a Bournes BP 200 infant ventilator. It was used as a constant flow generator, time cycled, rate 25 to 30 breaths per minutes, inspiratory:expiratory (I:E) ratio 1:1 or 1:2 with the flow rate (determinate of tidal volume) adjusted to maintain normocarbia. The mean airway pressure during CMV was varied by adjusting PEEP while holding tidal volume constant.

High frequency oscillations (HFO) (7) were generated by a piston pump with an adjustable stroke driven by a variable speed electric motor. Flow oscillations were transmitted to the endotracheal tube through a Silastic tube (i.d. 12 mm, length 0.7 m). A bias flow of fresh gas was provided from a variable orifice flowmeter through standard oxygen delivery tubing (i.d. 5 mm). This flow of gas delivered oxygen to and removed CO_2 from the top of the endotracheal tube. Excess fresh gas and CO_2 from the lung exited through an opening (i.d. 10 mm) to which a long tube (i.d. 10 mm, length 4.7 m) was attached to minimize loss of oscillation volume. This tubing is referred to as the low pass filter. Oscillation was performed with piston displacements set at 2 to 3 ml/kg, a frequency of 15 Hz and MAP adjusted by altering the flow of fresh gas (4 to 12 L/min). All studies with both CMV and HFO were done at $F_{I_{O_2}}$ 1.0.

Mean airway pressures on both ventilators were measured at the top of the endotracheal tube with a Validyne transducer model DP7, the output of which was passed through two cascaded, low pass, critically damped filters with a cut-off frequency of 0.05 Hz. During CMV raw airway pressures at this same point were determined with a Validyne transducer (D17).

Plethysmography

Plethysmographic studies were performed on 12 rabbits in total, six from each of two pulmonary injury models (lung lavage and oleic acid). The animals were studied in a 25-L Plexiglas constant volume plethysmograph with exit ports for the arterial line, endotracheal tube, and temperature probe. The pressure changes within the plethysmograph were sensed with a Validyne transducer (DP45). Frequency response of the entire system was determined by bursting balloons in the box. The resonant frequency was 100 Hz, with a flat response to 40 Hz. These parameters were adequate for the measurement of volume changes during CMV, but not for the oscillatory component of HFO volume changes. The box was statically calibrated using a 50-ml syringe as the volume signal. To avoid artifacts due to thermal drift, before each measurement the box was transiently opened to atmosphere. At the same time the airway was opened to atmosphere. The ventilatory condition of interest was then re-established and the volume change measured. Therefore, the lung volumes reported are always referenced to the animal's passive functional residual capacity (FRC) at the time of measurement.

The pressure signal (proportional to volume) from the box was integrated electronically. Integrator accuracy was verified by planimetry of a known input signal. The time-averaged volume signal derived by this method is reported as mean lung volume (MLV). An estimation of the error in MLV due to adiabatic phenomena was determined by ventilating a test lung in the plethysmograph with ventilatory parameters similar to those used for the rabbits. By filling the plethysmograph with SF6 (a gas with a high specific

heat and an adiabatic coefficient close to 1) adiabatic phenomena were minimized. During CMV measurements of MLV under these conditions were 5% higher than those found with an air-filled plethysmograph. Because of the small value for this difference, values for MLV on CMV are reported uncorrected. As the HFO volume signal is predominantly static, it represents an essentially isothermal process over time. What dynamic component there is, is both small and almost symmetrical. Consequently, the MLV reported for both modes of ventilation will have been negligibly affected by adiabatic phenomena.

Blood gas tensions were measured using a Corning 175 Auto-analyzer and were corrected for temperature.

Compliance curves of the lung thorax in the paralyzed rabbit were determined before and after induction of the lesion, using a calibrated syringe to vary volume and a Validyne transducer (D17) to measure pressure. Over a period of 60 seconds the lung was inflated to 30 cm H_2O in 5-ml increments then deflated in 5-ml decrements. The curves obtained by this method were identical with those obtained in the animal post mortem, using a slower cycling period of 2 minutes and preceded by three previous inflations to 30 cm H_2O.

Lung Lavage (Washed) Model

A surfactant depletion model of lung disease was induced in 12 rabbits as described by Lachman et al (8). After control arterial blood gas tensions were measured with both ventilators, the rabbits' lungs were lavaged with 100 ml of warm normal saline seven times, with the pulmonary distending pressure never exceeding 30 cm H_2O. Approximately 1 hour was then allowed for the lesion to stabilize during which time the rabbits were ventilated with CMV.

Oleic Acid Model

Pulmonary edema was induced in 10 rabbits by injection of 0.09 ml/kg of oleic acid. This was followed by a further 0.045 ml/kg if there was no significant deterioration in arterial blood gas tensions after 60 minutes. To maintain mean arterial pressure greater than 60 mm Hg and pH above 7.25, dextran and sodium bicarbonate were infused as necessary.

Once the lesions were established Pa_{O_2} was compared during periods of both HFO and CMV at various matched MAPs (8 to 24 cm H_2O). The order in which the ventilators were used was randomized. Because the lesions are inherently unstable, and our concern was primarily with oxygenation, blood samples for Pa_{O_2} measurement were obtained after 5-minute periods of ventilation. This interval, although brief, has been shown to be sufficient for Pa_{O_2} equilibrium (9, 10). After each pair of measurements we returned to the first ventilator used for that pair and repeated the measurements. The sequence was accepted for analysis only if the initial and final Pa_{O_2} values matched to within ± 10 torr. Care was taken to ensure that Pa_{CO_2} with the two modes of ventilation were matched.

Matched MLVs

In six animals the relationship of MLV to oxygenation was examined at various matched MAPs during CMV and HFO. Mean lung volumes, which were substantially lower during CMV at equivalent MAPs, were then matched for the two ventilatory modes by increasing the PEEP level during CMV, and blood gas tensions were compared.

Sustained Inflation

The effect of a sustained inflation on oxygenation was determined with both ventilators. During HFO this involved turning the oscillator off while leaving the bias flow to maintain the static distending airway pressure. The low pass filter was then progressively clamped until the level of airway pressure reached 30 cm H_2O where it was held for 10 to 15 seconds. The clamp was then removed, the airway pressure was allowed to decrease to its original value, and the oscillator was then restarted.

On CMV a sustained inflation was performed by placing the ventilator in its continuous positive airway pressure mode. This applied a pressure to the airway equivalent to the PEEP level during CMV. The expiratory limb of the ventilator tubing was then slowly clamped and the airway pressure allowed to increase to 30 cm H_2O and held there for 15 seconds. The clamp was then removed, MAP decreased to the working PEEP level, and CMV was resumed.

All results were analyzed using Student's *t*-test for paired data; p values < 0.05 were accepted as statistically significant.

Results

Lung Lavage Group

In the control period there were no significant differences in the Pa_{O_2} (420 ± 58 mm Hg vs 415 ± 48 mm Hg, or Pa_{CO_2} 36 ± 6 mm Hg vs 36 ± 6 mm Hg) during CMV or HFO.

A typical PV curve obtained in the control period

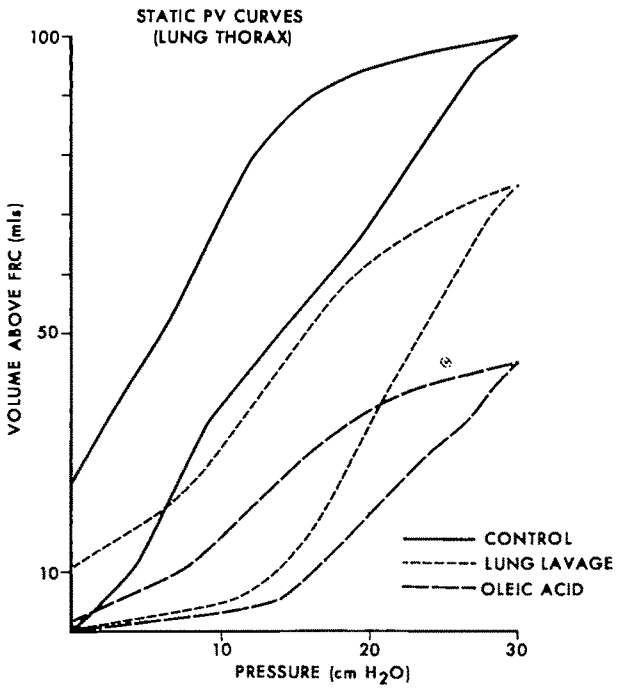


FIG 1. Typical in vivo pressure volume curves of respiratory system in control, lung lavage, and oleic acid lesions. Volumes reported are those greater than functional residual capacity (FRC).

and after lavage appears in Fig 1. Following serial pulmonary lavage, static lung thorax compliance (Crs) decreased from 6.1 ± 1.7 ml/cm H_2O to 3.1 ± 1.2 ml/cm H_2O ($p < 0.001$) and the opening pressure, defined as the airway pressure at the knee of the inflation limb, increased from 2.6 ± 1.3 cm H_2O to 15.1 ± 1.5 cm H_2O (Fig 2) ($p < 0.001$). Compliance of the steepest part of the inflation limb above opening pressure was 4.57 ± 1.19 ml/cm H_2O.

The time course of this particular pulmonary injury was such that after a ½- to 1-hour stabilization period, a 2- to 4-hour period of relative stability ensued. Thereafter, deterioration occurred in concert with progressively increasing amounts of clinically apparent frothy hemorrhagic edema. Pathologically the lesion was characterized by extensive hyaline membrane formation involving terminal small airways and associated with a variable amount of edema.

Gas Exchange at Matched MAPs. It soon became apparent that two distinct groups of results were generated depending upon where the working MAP fell with respect to opening pressure (Fig 2). At matched MAPs less than opening pressure, there was no difference between CMV and HFO in terms of oxygenation (41 ± 8 mm Hg vs 40 ± 7 mm Hg, n = 5) or mean lung volumes (18 ± 5 ml vs 21 ± 10 ml, n = 4) (Fig 2).

However, at matched MAPs greater than opening pressure, HFO resulted in superior oxygenation (Pa_{O_2} 228 ± 116 mm Hg vs 71 ± 42 mm Hg, $p < 0.001$, n = 18) (Fig 2), and significantly greater MLVs 58 ± 30 ml vs 29 ± 14 ml ($p < 0.005$, n = 8).

Matched MLV. When MLVs were matched with CMV and HFO, oxygenation was not significantly different (Pa_{O_2} 288 ± 160 mm Hg vs 265 ± 151 mm Hg). However, MAP was significantly greater during CMV compared with HFO (24.6 ± 4.9 cm H_2O compared with 15.3 ± 1.3 cm H_2O) ($p < 0.005$, n = 5).

Sustained Inflation. During HFO, a sustained inflation produced immediate improvements in MLV 30.9 ± 7.7 ml to 42.8 ± 5 ml, $p < 0.01$, n = 5) with concomitant and sustained improvements in gas exchange (Pa_{O_2} 115 ± 110 mm Hg to 291 ± 143 mm Hg, $p < 0.025$, n = 6) (Figs 3 and 4). Furthermore, the improvement in oxygenation was maintained for periods of up to 4 hours. In contrast a sustained inflation during CMV did not produce an increase either in lung volume or oxygenation.

Time Dependence. A progressive improvement in oxygenation at a fixed MAP could be repeatedly demonstrated during HFO (Fig 5) when examined over time intervals ranging from 10 to 60 minutes. The inherent progressive deterioration of the disease model made study over longer periods impossible.

Oleic Acid Group

Blood gas tensions were not significantly different before induction of the lesion during CMV and HFO (Pa_{O_2} 408 ± 43 mm Hg vs 407 ± 47 mm Hg; Pa_{CO_2} 37.6 ± 5.6 mm Hg vs 37.6 ± 5.6 mm Hg, n = 10). Fig 1 represents a typical PV curve after establishment of

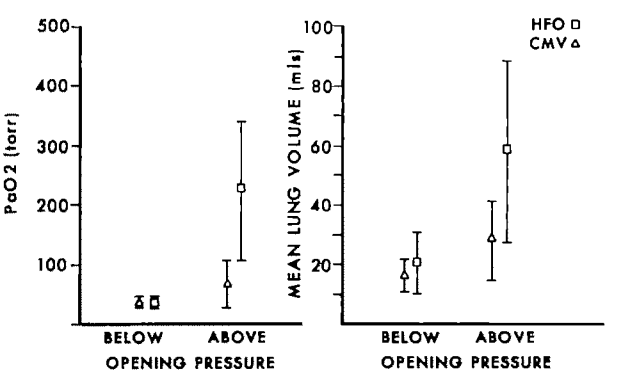


FIG 2. At matched MAPs in lung lavage model better oxygenation and lung volumes were achieved during HFO than during CMV if MAP was greater than opening pressure (n = 18 for Pa_{O_2}, n = 8 for MLV). At MAPs less than opening pressure there was no difference in these parameters between two modes of ventilation (n = 5 for Pa_{O_2}, n = 4 for MLV).

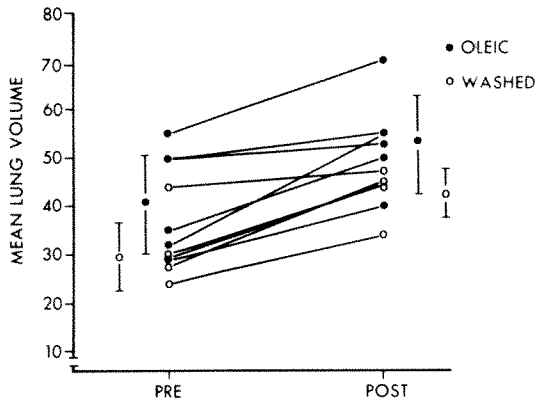


FIG 3. Typical changes in lung volume after sustained inflation (pre vs post) during HFO demonstrating significant increase with both lung models.

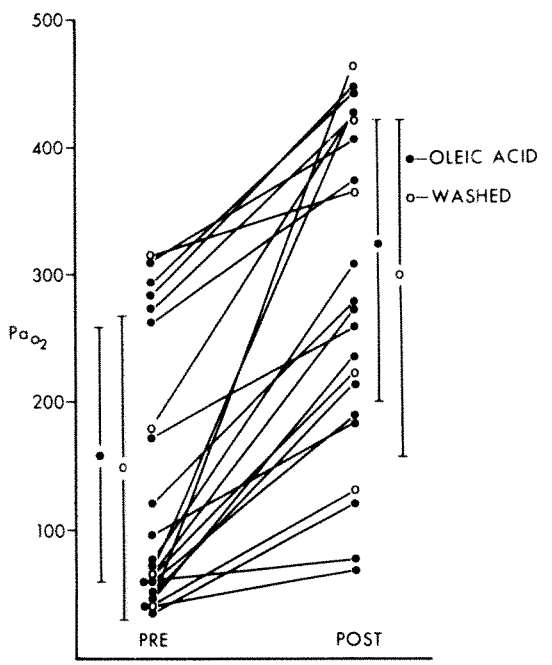


FIG 4. Responses of Pa_{O_2} to sustained inflation (pre vs post) during HFO with both models. There was always an increase in Pa_{O_2}. Variability in magnitude of change was function of individual lung's pathology and level of MAP at which maneuver was performed.

the lung lesion. The static compliances (Crs) decreased from 5.08 ± 1.3 ml/cm H_2O to 2.4 ± 1.0 ml/cm H_2O ($p < 0.001$). The compliance of the steepest part of the inflation limb of the PV curve above opening pressure was 2.7 ± 0.45 ml/cm H_2O. Unlike the surfactant depletion model, this lesion was more rapidly progressive with a 1- to 2-hour "stable" period after which a marked deterioration occurred.

Gas Exchange at Matched MAP. A significant advantage of HFO compared with CMV in terms of oxygenation at equivalent MAP could be demonstrated only at higher MAP (5 to 10 cm above opening pressure), Pa_{O_2} 256 ± 59 mm Hg vs 83 ± 45 mm Hg ($p < 0.05$). In contrast, at all matched MAPs compared above opening pressure HFO after the sustained inflation maneuver consistently yielded superior oxygenation and lung volume in comparison with CMV (Fig 6). After the sustained inflation maneuver the mean Pa_{O_2} value was 269 ± 116 mm Hg as compared with 116 ± 83 mm Hg ($p < 0.001$, n = 28) on CMV at the same MAP, and the MLV achieved was 45 ± 15 ml vs 30.9 ± 13 ml ($p < 0.001$, n = 15).

Matched MLVs. In two animals, attempts were

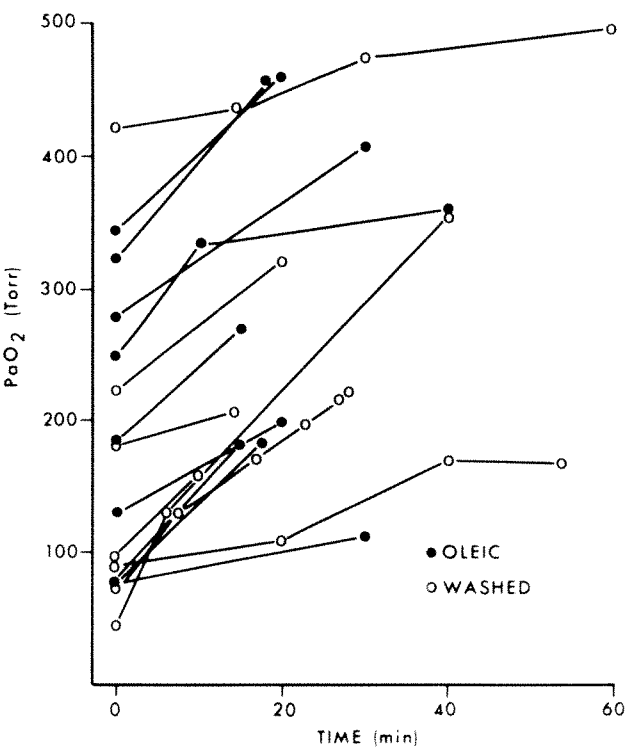


FIG 5. Time course of Pa_{O_2} during HFO (in both lesions, pre- and post-sustained inflation included).

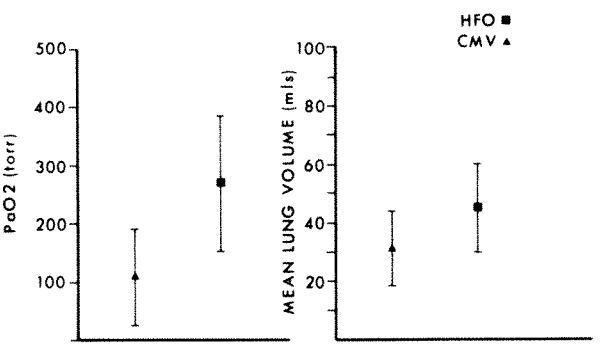


FIG 6. Comparative Pa_{O_2} (n = 18) and lung volumes (n = 15) during HFO and CMV in oleic acid model at equivalent MAP. HFO values are post-sustained inflation.

made to equate MLVs during CMV and HFO by increasing MAP during CMV. In both instances tension pneumothoraces resulted, leading to the rapid demise of each animal.

Sustained Inflation. The matched comparisons of HFO and CMV in Fig 6 were always made after having performed a sustained inflation during HFO. In addition, separate observations of the impact of the sustained inflation during HFO and CMV were made. Dramatic improvements were only observed during HFO with an increase in oxygenation (Pa_{O_2} 134 ± 102 mm Hg to 274 ± 124 mm Hg, $p < 0.001$, n = 17) and MLV (41.8 ± 11 ml to 53.8 ± 9.7 ml, $p < 0.01$, n = 6).

Time Dependence. An improvement in arterial oxygenation over time could often be demonstrated during HFO (Fig 5). In view of the instability of the pulmonary lesion, the time course of improvement could only be examined over much shorter time periods (10 to 30 minutes) than in the lavaged lung model.

Tidal volumes determined by plethysmography varied between 10 to 15 ml/kg during CMV and 2 to 3 ml/kg during HFO.

Discussion

This study demonstrates that HFO can achieve sustained increases of oxygenation and lung volume in two diverse models of lung disease. Tactically this has proved possible because the unusual properties of HFO allow gas exchange to occur with small phasic volume swings. This allows maintenance of a constant lung volume at or near optimal values throughout the respiratory cycle, the aim being maximal recruitment of alveolar volume with minimal overdistention.

Two different models of lung disease were used. Oleic acid produces a capillary leak with hemorrhagic pulmonary edema which was generally progressive. The lung lavage produces a model of surfactant deficiency with hyaline membranes in the terminal airways; it is relatively stable although with time pulmonary edema does appear.

The relationships between lung volume, oxygenation, and volume history have been studied by Anthonisen (11) in the normal lung. During incremental inflation of the degassed lung in vivo Anthonisen demonstrated a linear decrease in $\dot{Q}s/\dot{Q}t$ with increases in lung volume (up to 70% total lung capacity), suggesting progressive recruitment of alveoli with a wide range of opening pressures. During deflation from total lung capacity, $\dot{Q}s/\dot{Q}t$ was insensitive to change in lung volume, suggesting that in the normal lung gas exchanging units once recruited were stable and markedly resistant to collapse. Furthermore, once the degassed lung has been re-expanded $\dot{Q}s/\dot{Q}t$ was independent of lung volume for volume excursions in the tidal range. Anthonisen concluded that surface forces rather than recruitment/derecruitment of air spaces are largely responsible for PV hysteresis in the normal lung.

However, in the diseased lung, Nelson and Olsen (12) have suggested that, due to alveolar instability, recruitment and derecruitment become important contributors to PV hysteresis in the tidal range. Analogous to Anthonisen's studies with the degassed lung (11), one should be able to show a progressive, but not necessarily linear, recruitment of gas exchanging air space with increases in airway pressure. This recruitment may occur because of either opening airways or alveoli, or redistribution of intra-alveolar edema fluid (13). But more important, during deflation, unlike the normal lung, $\dot{Q}s/\dot{Q}t$ should be sensitive to lung volume to the extent that progressive derecruitment of unstable air spaces occurs as volume decreases. Furthermore, $\dot{Q}s/\dot{Q}t$ should be lower on deflation than on inflation to the extent that these unstable air spaces exhibit hysteresis. During HFO these relationships can be exploited by using the sustained inflation to provide opening forces to position the lung on its deflation limb.

Ventilatory Pattern and Oxygenation. In both models we were able to demonstrate an improvement in Pa_{O_2} during HFO compared with CMV at equivalent MAP, provided the MAP chosen was high enough. The level of MAP chosen was critical for it determined gas exchanging surface area.

The PV curve of the washed lung exhibits a marked improvement in compliance above opening pressure (Fig 1). If analogous to the normal lung this is secondary to the recruitment of a large cohort of airspaces that have opening pressures in this range (14). In our studies during HFO this recruitment is reflected in the marked increase in Pa_{O_2} at MAPs just greater than opening pressure. In contrast, the oleic acid model had a much smaller change in slope at opening pressure (mean slope beyond opening pressure 2.7 vs 4.6 ml/cm H_2O for the lavaged lung model) (Fig 1). This was reflected in the absence of a marked improvement in Pa_{O_2} and presumably recruitment of air space, by oscillating at MAPs just greater than opening pressure. In this model, by using MAP 5 to 10 cm H_2O greater than opening pressure, it was possible to recruit sufficient air space so that significant improvements in oxygenation during HFO compared with

CMV at the same MAP were achieved.

At matched MAPs, CMV results in lower lung volume and inferior oxygenation compared with HFO (Fig 2). Photographs (Figs 7 and 8) of the excised lung during both modes of ventilation at equivalent MAP suggest an explanation. During CMV (Fig 7) the lung cycles between distention (Fig 7, right) and extensive atelectasis (Fig 7, left). This atelectasis at end expiration occurs despite the presence of a PEEP of 9 cm H_2O insufficient to prevent large amounts of air space closure. Thus, during the majority of the respiratory cycle the lung is at a disadvantageous volume for gas exchange (15). In contrast, during HFO at the same MAP the lung remained distended throughout the cycle (Fig 8, left) and at no point demonstrated the extensive atelectasis present with CMV during expiration. In the intact animal, this is reflected in the improved MLV and oxygenation achieved with HFO.

Thus, in these two models, provided MAP is high enough, there appears to be an advantage to maintaining that pressure constant throughout the ventilatory cycle (as with HFO) rather than distributing it in a phasic manner as is done with CMV, the former strategy minimizing closure of air space throughout the respiratory cycle.

Sustained Inflation. Attempts to improve oxygenation during CMV by intermittent sustained inflations have been made in patients with lung disease, but without clinical benefit (6). We have similarly found no improvement in either lung volume or oxygenation after a sustained inflation during large tidal volume CMV. Our studies suggest that sustained inflation during CMV with PEEP does not result in recruitment of a lung volume significantly larger at end expiration than that already recruited by a series of large tidal volume breaths (Fig 9, B). The limiting factor in the recruitment and maintenance of volume during this form of ventilation appears to be the end-expiratory pressure rather than the opening forces. If distribution of lung volume recruited by the sustained inflation vs

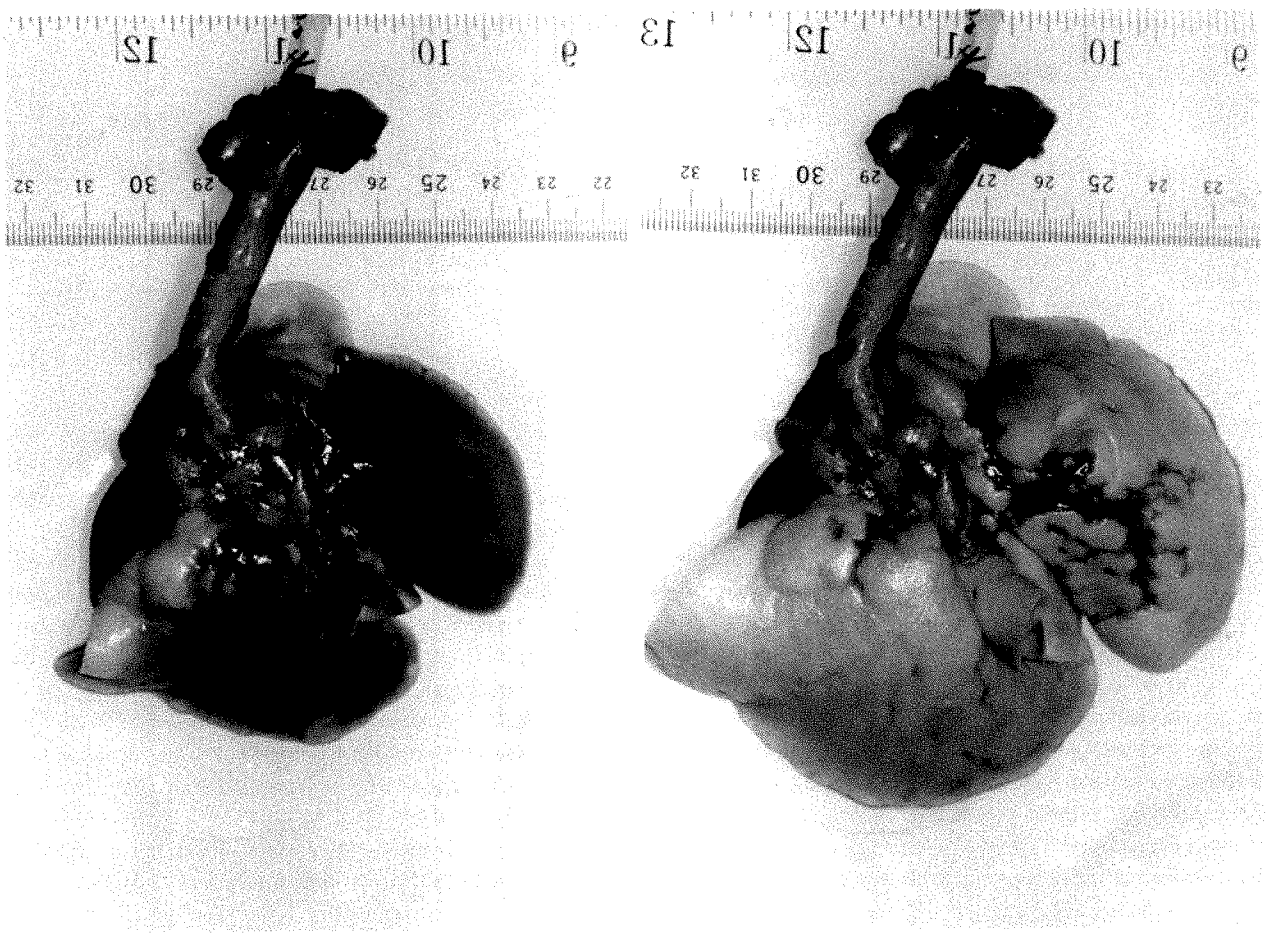


FIG 7. Excised lung of lung lavage model during CMV. Left, During end expiration (PEEP 9 cm) exhibiting marked atelectasis; right, at peak inflation.

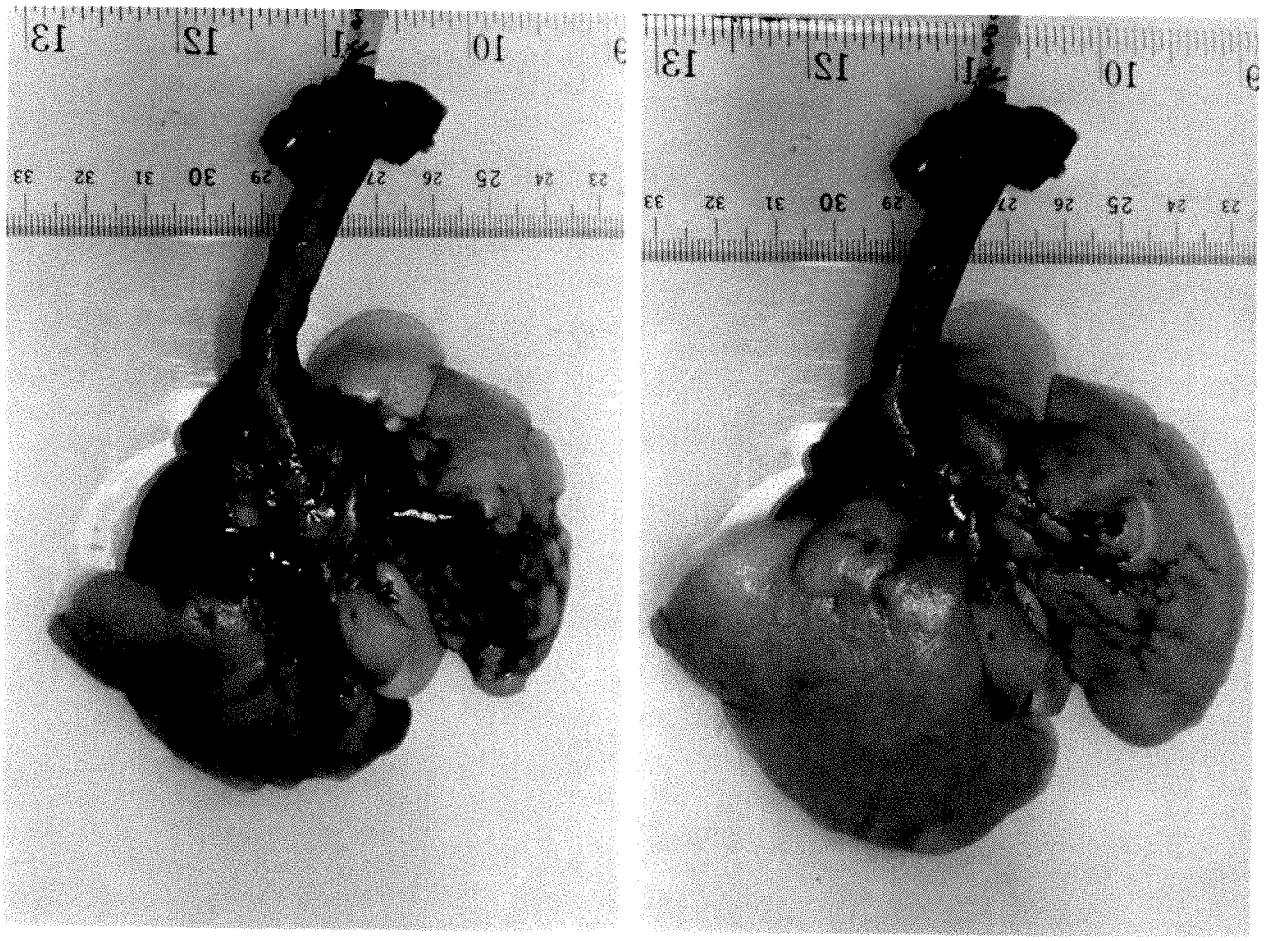


FIG 8. Same lung as shown in Fig 7 during HFO at same MAP as in Fig 7. Left, Lung during HFO with no preceding sustained inflation. Lung volume is intermediate between both parts of Fig 7 and does not demonstrate extensive atelectasis of Fig 7, left. Right, Lung at same MAP after sustained inflation, demonstrating marked increase in lung volume and decrease in atelectasis compared with lung shown on left.

large tidal volume CMV is different, it is not reflected by an improvement in Pa_{O_2}.

In contrast, during HFO, sustained inflation with both lung models resulted in dramatic increases in Pa_{O_2} and lung volume (Figs 8 and 9, A). These increases in Pa_{O_2} and MLV after a sustained inflation occurred because the sustained inflation provided the large opening forces that are otherwise absent with the low volume oscillatory excursions of HFO. During CMV, these opening forces are provided by the series of large tidal volume breaths.

The strikingly higher MLVs and superior oxygenation achieved with HFO following sustained inflation compared with CMV are due to the ability of HFO to maintain a greater fraction of the air spaces recruited by a sustained inflation open than CMV operating at the same MAP. The critical difference between HFO and CMV occurs during the expiratory phase of CMV. From Fig. 7, it is seen that with CMV much of the volume recruited during inspiration is not maintained during expiration, i.e., diseased units have high closing pressures and conventional levels of PEEP (9 cm in this example) fail to prevent massive closure of the recruited alveoli.

In contrast, with HFO the presence of a continuous distending pressure on the lung essentially equivalent to MAP prevents the closure of a significantly larger fraction of the alveoli recruited by sustained inflation (Fig 9, A). Again, it is the absence of the minima in end-tidal lung volume present during CMV that accounts for the superiority of HFO. The MAP acts as super PEEP, but with a method for CO_2 removal provided by HFO.

There was considerable variation in the magnitude of improvement after the sustained inflation as a result of differences in the lung mechanics and level of MAP used in each particular case. The improvement in Pa_{O_2} was immediate and maintained for pe-

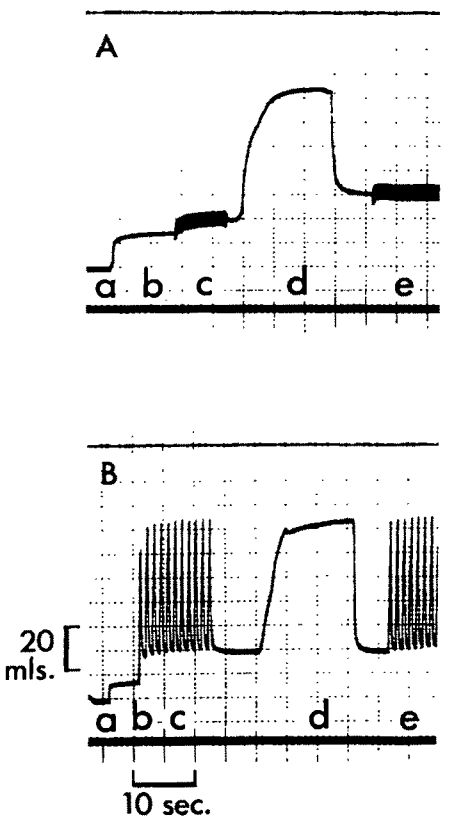


FIG 9. Plethysmograph trace in lung lavage model demonstrating effect of sustained inflation on lung volume during HFO (A) compared with CMV (B) both at same MAP (15 cm H_2O). a, Airway and plethysmograph open to atmosphere—zero volume, thus subsequent volumes are those greater than FRC; b, lung volume with ventilator attached to airway—airway pressure is end-expiratory level for both ventilators (9 cm for CMV, 13 cm for HFO); c, ventilator on for 10-second period; d, sustained inflation maneuver; e, ventilation resumed.

riods of up to 1 hour. Progression of the lesion precluded the definition of time course for longer periods.

The improvement in oxygenation during HFO seems generally to coincide with the increase in lung volume. However, recruitment may not be the only mechanism for the improved oxygenation. If the mechanism of gas exchange during HFO is facilitated diffusion, gas will travel along concentration gradients and be independent of regional compliance (16). Another possibility is redistribution of edema fluid. Particularly toward the end of the oleic acid experiments, large amounts of foamy hemorrhagic edema fluid came up the endotracheal tube and expiratory limb of the ventilator during CMV. This was never seen during HFO.

In addition to this immediate improvement in Pa_{O_2} with HFO, there was generally a time-dependent progressive increase in Pa_{O_2}. We assume that this represents continued recruitment of alveoli but could not prove this because of thermal drift in the plethysmograph. This recruitment may result from the oscillatory pressure swings "shaking" open the lung or it may simply be the result of the sustained mean pressure. This "creep" varied considerably in rate and magnitude and was not always present, particularly if the lung lesion became progressively more severe.

Matched Lung Volumes. In the lung lavage model, blood gas tensions during CMV could be made to match those of the oscillator by increasing PEEP and, of necessity, peak lung volumes and pressures to achieve adequate convective flow for CO_2 removal, but under these circumstances MAP was approximately 10 cm higher than on the oscillator. In the oleic acid model, attempts to match MLV and blood gas tensions during CMV were disastrous. Elevating PEEP resulted in substantial increases in peak and mean airway pressures. In both animals in which this was attempted, large pneumothoraces developed so that subsequent attempts to match lung volume were abandoned.

Volume of Oscillations during HFO. We do not know accurately how much volume is being delivered to the lung. The piston displacement is dissipated partially as compression volume and part is lost down the low pass filter. Peak-to-peak pressure excursions in the plethysmograph indicate a volume of 2 to 3 ml/kg. Comparison of the plethysmograph volumes generated with sinusoidal calibration signals from a leak-free piston at 0.1 and 15 Hz suggest that at 15 Hz the volume is over-estimated by 10% to 20%. A hot wire anemometer (17) calibrated with a 15-Hz unidirectional square wave signal and positioned at the top of the endotracheal tube also suggests a volume of approximately 2 ml/kg, but the validity of this device at 15 Hz with an unknown flow profile is questionable.

Frequency. There is nothing magic about 15 Hz. We get equally satisfactory gas exchange at 40 Hz. We have not studied the efficacy of these strategies at lower frequencies.

Cardiovascular Effects. The effects on the cardiovascular system of recruiting alveolar volumes with these strategies during HFO were not studied in detail. In several instances, most marked in the lung lavage model, when, after sustained inflation, effective lung compliance improved secondary to recruitment, increased transfer of airway pressure to the pleural space (as reflected by increased pleural pressures) was observed. In the volume-depleted animal this coincided with a decrease in blood pressure. Blood pres-

sure could be restored in such cases, however, by fluid infusion.

This study has some important general points with regard to standard ventilator therapy. PEEP was introduced to increase the end-expiratory lung volume; however, its effectiveness in maintaining end-expiratory volume and oxygenation is limited by the number of alveoli whose closing pressures are exceeded by that value of PEEP. Thus, super PEEP (18) is used by a number of groups to increase the number of alveoli recruited. However, gas transport by bulk flow requires that large phasic volume changes be superimposed. This leads to large peaks in lung volume, and, furthermore, uneven distribution of these large phasic volumes because of time-constant inhomogeneity in the diseased lung results in overdistention of some alveoli with the possible consequences of alveolar rupture and increased pulmonary vascular resistance in these areas (19).

Gattinoni et al (20) have used an approach conceptually similar to the one we describe. They use apneic oxygenation with a MAP of 10 to 15 cm H_2O and eliminate CO_2 via a partial bypass through a membrane lung. Essentially we are doing the same thing except that we are eliminting CO_2 by facilitated diffusion.

In conclusion, on standard mechanical ventilation, oxygenation depends on the F_{IO_2} and the mean airway pressure. However, if the end-expiratory pressure is lower than "closing pressure" there will be atelectasis during much of the respiratory cycle. To overcome this, high end-expiratory pressure must be used. Superimposition of large tidal volume ventilation results in high mean and peak pressures and increased risk of barotrauma. With high frequency oscillations large volume swings are not required to eliminate CO_2. Therefore mean airway pressure greater than closing pressure can be used, leading to substantial volume recruitment and improved oxygenation with less risk of barotrauma.

ACKNOWLEDGMENT

We are grateful to the Bourns Company for the loan of a Bourns 200 ventilator for the duration of our studies.

REFERENCES

1. Cheney FW, Martin WE. Effects of continuous positive-pressure ventilation on gas exchange in acute pulmonary edema. J Appl Physiol 1971;30:378–81.
2. Herman S, Reynolds EOR. Methods for improving oxygenation in infants mechanically ventilated for severe hyaline membrane disease. Arch Dis Child 1973;48:612–7.
3. Boros SJ, Maralon SV, Ewald R, et al. The effect of independent variations in inspiratory-expiratory ratio and end expiratory pressure during mechanical ventilation in hyaline membrane disease: the significance of mean airway pressure. J. Pediatr 1977;91:794–8.
4. Boros SJ. Variations in inspiratory:expiratory ratio and airway pressure wave form during mechanical ventilation: the significance of mean airway pressure. J Pediatr 1979;94:114–7.
5. Hoppin FG, Hildebrandt J. Mechanical properties of the lung. In: West JB, ed. Bioengineering aspects of the lung. New York: Marcel Dekker Inc, 1977:83–162.
6. Housley E, Louzada N, Backlake MR. To sigh or not to sigh. Am Rev Respir Dis 1970;101:611–4.
7. Butler WJ, Bohn DJ, Bryan AC, Froese AB. Ventilation by high-frequency oscillation in humans. Anesth Analg 1980;59:577–84.
8. Lachmann B, Robertson B, Vogel J. In vivo lung lavage as an experimental model of the respiratory distress syndrome. Acta Anaesthesiol 1980;24:231–6.
9. Nunn JF. Applied respiratory physiology. 2nd ed. Boston: Butterworths, 1978:412–4.
10. Rose DM, Downs JB, Heenan TJ. Temporal responses of functional residual capacity and oxygen tension to changes in positive end-expiratory pressure. Crit Care Med 1981;9:79–82.
11. Anthonisen NR. Effect of volume and volume history of the lungs on pulmonary shunt flow. Am J Physiol 1964;207:235–8.
12. Neilson D, Olsen DB. The role of alveolar recruitment and derecruitment in pressure-volume hysteresis in lungs. Respir Physiol 1978;32:63–77.
13. Malo J, Ali J, Duke K, Gallagher W, Wood LDH. How does PEEP reduce Qs/Qt in pulmonary edema. Fed Proc 1980;39: 280.
14. Glaister DH, Schroter RC, Sudlow MF, et al. Bulk elastic properties of excised lungs and the effect of a transpulmonary pressure gradient. Respir Physiol 1973;17:347–64.
15. Kirby RR. Mechanical ventilation in acute ventilatory failure: facts, fiction and fallacies. Curr Probl Anesth & Crit Care Med 1977;1:1–39.
16. Fredberg JJ. Augmented diffusion in the airways can support pulmonary gas exchange. J Appl Physiol 1980;49:232–8.
17. Yoshiya I, Nakajima T, Nagai I, et al. A bidirectional respiratory flowmeter using the hot-wire principle. J Appl Physiol 1975;38: 360–5.
18. Kirby RR, Downs JB, Givetta JM, et al. High level positive end-expiratory pressure (PEEP) in acute respiratory insufficiency. Chest 1975;67:156–63.
19. Suter PM, Fairley HB, Isenberg MD. Effect of tidal volume and positive end-expiratory pressure on compliance during mechanical ventilation. Chest 1978;73:158–62.
20. Gattinoni I, Pesenti A, Rossi GP, et al. Treatment of acute respiratory failure with low-frequency positive-pressure ventilation and extracorporeal removal of CO_2. Lancet 1980;2:292–4.

ANESTH ANALG
1982;61:333-7

Reduction of Hypoxic Ventilatory Drive by Dopamine

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WARD, D. S., AND BELLVILLE, J. W.: Reduction of hypoxic ventilatory drive by dopamine. Anesth Analg 1982;61:333-7.

To define precisely the effects of dopamine on hypoxic ventilatory drive, two sets of experiments were performed in five healthy subjects. End-tidal CO_2 was held constant in all experiments. First, a dopamine infusion (3 μg/kg/min) was started in subjects already rendered hypoxic, causing an average sustained decrease in ventilation to 60% of the preinfusion ventilation. In the second group of experiments, the ventilatory response of subjects made hypoxic during a dopamine infusion was compared with the hypoxic ventilatory response without the dopamine infusion. Without dopamine, a sudden decrease in end-tidal O_2 from 100 to 53 torr caused ventilation to increase from 11.9 to 20.9 L/min ($p < 0.01$). During the dopamine infusion, only a statistically insignificant increase in ventilation (9.8 to 12.8 L/min) was seen with the same hypoxic stimulus. Low dose dopamine is a potent depressant of hypoxic ventilatory response.

Key Words: VENTILATION: dopamine; PHARMACOLOGY: dopamine.

DOPAMINE is a neurotransmitter which, in the carotid bodies of several species (1), functions as a modulator of that organ's response to hypoxia and hypercapnia (2). Exogenously administered dopamine presumably acts on the same receptors as the natural neurotransmitter. Clinically, dopamine is frequently used to provide inotropic support in critically ill patients. It has been observed to decrease the arterial P_{O_2} (3, 4) and it also appears to blunt the respiratory response to hypoxia (5, 6).

Patients dependent on hypoxic drive do not increase their ventilation in response to an elevation of arterial carbon dioxide tension (7). In these patients, depression of the hypoxic drive by dopamine will not be compensated by a ventilatory response secondary to an increase in carbon dioxide tension. In normal subjects the magnitude of ventilatory depression caused by dopamine may be masked by the response to increased carbon dioxide. To simulate in normal subjects the effect of dopamine in patients dependent on hypoxic drive, we controlled end-tidal carbon dioxide so that it did not increase during dopamine-induced respiratory depression. Thus, the respiratory stimulation that would be seen in normal subjects from increased carbon dioxide was eliminated. Any resulting respiratory depression would then be representative of that expected in patients dependent on hypoxic drive mediated by their carotid bodies.

Methods

Five healthy male subjects, aged 18 to 25 years, were studied, and all experimental protocols were approved by the UCLA Human Subject Protection Committee. The subjects were allowed their usual meals but were asked to refrain from coffee, tea, cola, alcoholic beverages, and marijuana for 12 hours before the experiment. All subjects were free of medical problems by history and physical examination; their chest roentgenogram, electrocardiogram, and serum chemistries were normal. The subjects were naive to respiratory physiology as well as to the expected effects of dopamine.

During the experiment, the subjects were seated and electrocardiogram (ECG) and blood pressure were monitored. The subjects breathed through a low dead-space valve (Rudolph P-320) from a gas mixing chamber where the concentration of CO_2 and O_2 could be adjusted on a breath-by-breath basis as described below. End-tidal CO_2 was measured with a Beckman LB-2 infrared analyzer, O_2 with an Applied Electro-Chemistry fuel cell analyzer (S-3A); exhaled flow was measured with a mass flowmeter (Thermo System model 1054B). Tidal volume (BTPS) was derived from

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Supported by a grant from the Department of Anesthesiology, University of California, Los Angeles.
Received from the Department of Anesthesiology, University of California, Los Angeles, School of Medicine, Los Angeles, California 90024. Accepted for publication December 18, 1981.
Reprint requests to Dr. Ward.

the flow signal by electronic integration. Arterial O_2 saturation was monitored by ear oximetry (Hewlett-Packard model 47201A). These data were collected on a floppy disc by a PDP/8e computer and also displayed on a strip chart recorder.

A computer-controlled mixing chamber manipulated the inspired concentration of CO_2 and O_2 to achieve the desired end-tidal gas conditions. A combination of feedback control and feed-forward control, via an empirical model, was used in the dynamic end-tidal forcing technique to control end-tidal gas tensions independent of the ventilatory response and of the gas tensions in mixed venous blood (8).

A freely running saline infusion was used in all experiments. Dopamine (Intropin, American Critical Care) was infused into the intravenous line as a 400-mg/L solution in normal saline. The rate of infusion was controlled with a Harvard syringe infusion pump to achieve a dose of 3 μg/kg/min of dopamine. The subjects were unaware of when the dopamine was started or stopped. Although a dose-response curve was not performed, we attempted to use a relatively low dose of dopamine so that primarily dopamine receptors would be stimulated, without affecting other adrenergic receptors.

Two sets of experiments were performed. In the first set, four subjects were used for steady-state hypoxic tests. After five minutes of breathing a hypoxic mixture ($P_{ET}O_2$ = 55.5 ± 1.7 torr; arterial saturation, S_{O_2} = 92.1% ± 1.3%, intersubject mean ± standard error), each subject received a dopamine infusion at a rate of 3 μg/kg/min which was continued for 5 minutes. The infusion was then terminated and data were collected for 5 additional minutes. Throughout the experiment, end-tidal CO_2 was held constant at slightly hypercapnic levels ($P_{ET}CO_2$ = 42.9 ± 0.9 torr). The mild hypercapnia permitted better control of the end-tidal CO_2.

The data were collected on a breath-by-breath basis. For each subject, the ventilatory data were averaged over the last 2 minutes before the start of the infusion and for the last 2 minutes of the dopamine infusion. The ventilation increased after the termination of the infusion but did not reach a steady state by the end of the 5-minute data collection period. Thus no averages were made in this period.

The second set of experiments utilized five subjects for hypoxic step tests. Fourteen hypoxic steps were made during saline infusion; nine hypoxic steps were made during dopamine infusion (3 μg/kg/min). Nine saline-infusion and seven dopamine-infusion experiments were suitable for analysis; the others were discarded because of data collection equipment malfunction or extremely irregular breathing. A 5-minute normoxic period was followed by a sudden decrease in inspired oxygen concentration to the hypoxic level ($P_{ET}O_2$ = 53.1 ± 0.1 torr; S_{O_2} = 88.1% ± 0.7%) for 5 minutes, with a 5-minute normoxic recovery period. Throughout the experiments, end-tidal CO_2 was held constant ($P_{ET}CO_2$ = 42.6 ± 0.4 torr).

These data were summarized by averaging on a breath-by-breath basis over the last 2 minutes of the normoxic period, the last 2 minutes of the hypoxic stimulation period, and for the last 2 minutes of the 5-minute recovery period. The data collected for all subjects during the saline infusions were then averaged, as were the data collected during the dopamine infusions.

Results

Steady-State Hypoxia Experiments

After the dopamine infusion was begun, there was an immediate reduction in tidal volume in all four subjects (Fig 1). This reduced ventilation was maintained at a mean of 60% ($p < 0.05$) of the preinfusion ventilation and no biphasic responses were seen. The ventilation, $P_{ET}CO_2$, $P_{ET}O_2$, and S_{O_2} for each subject are given in Table 1. During the infusion, the $P_{ET}CO_2$ was slightly higher (average 0.7 torr) and the $P_{ET}O_2$ was slightly lower (average 1.1 torr) in all cases. These small changes in the end-tidal partial pressures may

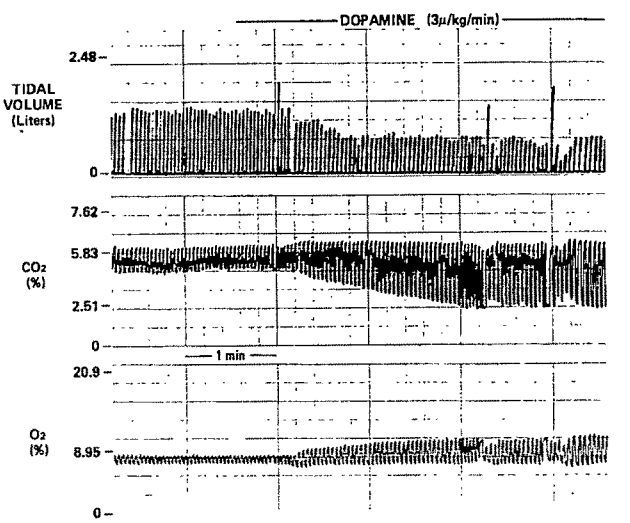


FIG 1. Ventilation response of one subject to dopamine infusion during steady-state hypoxia as shown in strip chart recording of breath-by-breath tidal volume and airway CO_2 and O_2 concentrations. Inspired CO_2 and O_2 concentrations were adjusted to maintain constant end-tidal values throughout experiment. Period of dopamine infusion is indicated. A rapid, sustained reduction in tidal volume is seen after dopamine infusion was started.

cause a small increase in ventilation and would result in an underestimation of the dopamine action.

Hypoxic Step Experiments

The results of the end-tidal hypoxic step experiments, with and without dopamine infusion are summarized in Table 2.

In the experiments during saline infusion only, end-tidal P_{O_2} was manipulated from approximately 100 to 53 torr, and back to 100 torr. Despite attempts to hold end-tidal P_{CO_2} constant, the normoxic period had a slightly (<1 torr) but consistently higher P_{ETCO_2}. In response to this isocapnic hypoxic stimulus, the minute ventilation increased by 9 L/min. However, in the recovery period, the minute ventilation, although less than the hypoxic-induced ventilation, was still greater than during the normoxic period.

In the hypoxic step experiments during dopamine infusion, P_{ETO_2} was manipulated in a similar manner. There was no significant change in the P_{ETCO_2} throughout the experiment. However, the minute ventilation, although increasing slightly during the hypoxia in a few subjects, on the average made no significant increase. The recovery ventilation was not different from either the normoxic or the hypoxic period.

Fig 2 presents experiments done on one subject with a saline infusion and with a dopamine infusion. The end-tidal P_{O_2}, P_{CO_2}, and oxygen saturation by ear oximetry are shown. The inspired gas concentrations used to obtain these end-tidal values are not shown. In the saline infusion experiment (Fig 2, left) there is a brisk response to hypoxia. This response is almost completely abolished during dopamine infusion (Fig 2, right).

TABLE 1
Ventilatory Response to Dopamine Infusion during Hypoxia*

Subject	$\dot{V}$	PET_{CO_2}	PET_{O_2}	S_{O_2}
	L/min	*torr*		%
1 Predopamine (N = 55)	15.4 ± 2.3	41.0 ± 0.4	53.3 ± 1.1	—
Dopamine (N = 50)	9.3 ± 2.1	41.5 ± 1.0	52.5 ± 2.3	—
2 Predopamine (N = 29)	16.9 ± 2.8	44.5 ± 0.6	61.4 ± 1.6	95.0 ± 0.7
Dopamine (N = 24)	12.0 ± 5.0	45.6 ± 1.3	60.5 ± 3.5	92.9 ± 0.6
3 Predopamine (N = 38)	43.4 ± 3.5	44.2 ± 0.3	54.2 ± 1.4	91.5 ± 1.1
Dopamine (N = 39)	25.8 ± 3.0	44.5 ± 0.3	51.9 ± 0.9	89.2 ± 0.6
4 Predopamine (N = 46)	36.6 ± 8.4	42.0 ± 0.6	53.1 ± 0.6	89.7 ± 0.8
Dopamine (N = 45)	18.5 ± 6.7	42.8 ± 1.2	52.7 ± 2.2	87.6 ± 1.0

* Dopamine was infused for 5 minutes during steady-state hypoxia. Ventilatory data were obtained by breath-by-breath averages for the last 2 minutes before the start of the dopamine infusion and for the last 2 minutes of the dopamine infusion (3 μg/kg/min). Values are means ± SD; N = number of breaths averaged. Saturation data are not available for subject 1.

TABLE 2
Averaged Data for Hypoxic Step Experiments*

	Normoxia	Hypoxia	Recovery (normoxia)	Normoxia-hypoxia	Hypoxia-recovery	Normoxia-recovery
Saline infusion (N = 9)						
$\dot{V}$ (L/min)	11.9 ± 0.8	20.9 ± 1.7	14.5 ± 1.1	$p < 0.01$	$p < 0.01$	$p < 0.01$
End-tidal P_{O_2}(torr)	100.3 ± 0.9	53.0 ± 0.1	99.7 ± 0.8	$p < 0.01$	$p < 0.01$	NS
End-tidal P_{CO_2}(torr)	42.9 ± 1.0	42.3 ± 0.9	42.3 ± 1.0	$p < 0.01$	NS	$p < 0.01$
S_{O_2} (%) (N = 8)	97.8 ± 0.5	88.9 ± 0.9	97.4 ± 0.4	$p < 0.01$	$p < 0.01$	NS
Dopamine infusion (N = 7)						
$\dot{V}$ (L/min)	9.8 ± 2.0	12.8 ± 0.9	12.6 ± 1.1	NS	NS	NS
End-tidal P_{O_2}(torr)	100.9 ± 1.5	53.1 ± 0.2	99.6 ± 1.1	$p < 0.01$	$p < 0.01$	NS
End-tidal P_{CO_2}(torr)	43.0 ± 1.1	42.6 ± 1.2	42.5 ± 1.3	NS	NS	NS
S_{O_2} (%) (N = 6)	97.4 ± 0.5	88.9 ± 1.1	97.6 ± 0.5	$p < 0.01$	$p < 0.01$	NS

* Breath-by-breath data for each experiment were averaged for the last 2 minutes of the 5-minute normoxic period, last 2 minutes of hypoxic period, and last 2 minutes of 5-minute normoxic recovery period. Values are average ±SE of different subjects (N = number of experiments). Intrasubject (breath-by-breath) variability is not considered, but it is small compared with intersubject variability. Last three columns give statistical significance for differences between indicated periods (Student's paired *t*-test; NS, not significant at 0.01 level).

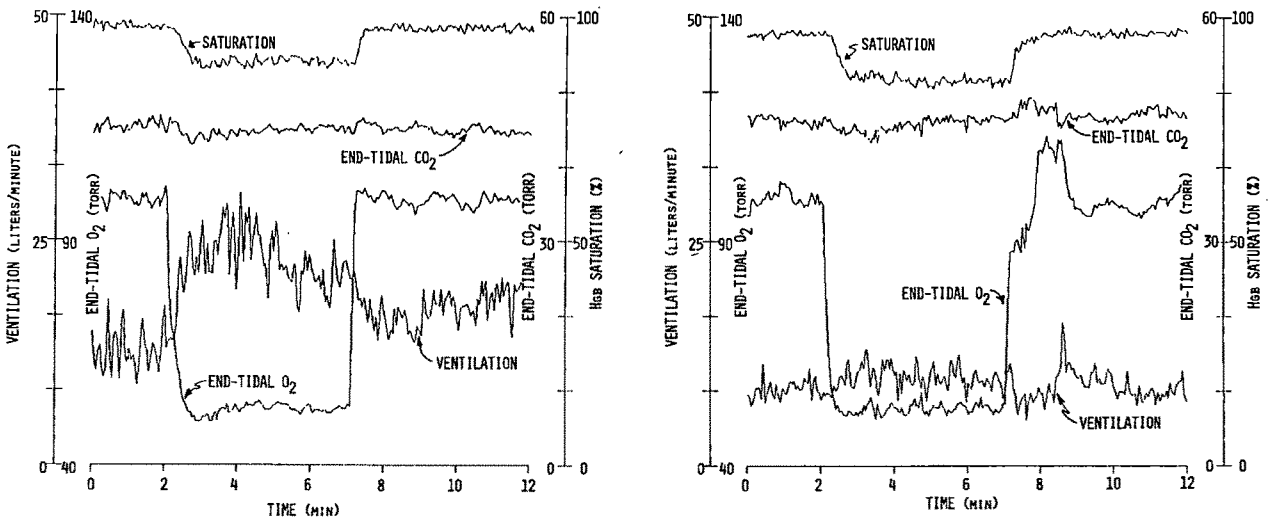


FIG 2. Ventilatory response of one subject to a step decrease in end-tidal O_2: left, saline infusion; and right, dopamine infusion (3 μg/kg/min). Breath-by-breath data are plotted by computer. Rapid decrease in end-tidal O_2 tension was caused by a sudden decrease in inspired O_2 concentration (not shown). End-tidal CO_2 tension was held constant by manipulating inspired CO_2 tension (not shown). Ear oximeter saturation measurement was made on a breath-by-breath basis. Brisk response in minute ventilation (calculated for each breath) is seen with saline (left) and is eliminated by the dopamine infusion (right).

Discussion

Depending on the dose (9), dopamine has different pharmacologic effects. With the low dose range (<5 μg/kg/min) that we studied, dopamine has some inotropic effect and increases renal perfusion (10). The effect on renal blood flow has prompted much of dopamine's clinical use. Pharmacologically, dopamine, in this dose range, acts primarily on dopaminergic receptors (5). At higher concentrations it also acts on alpha- and beta-adrenergic receptors. As stimulation of alpha- and beta-adrenergic receptors is known to affect ventilation, ventilatory effects of higher doses of dopamine are difficult to interpret in terms of action on dopamine receptors. We did not perform a dose-response curve for dopamine as we were interested only in dopamine receptor stimulation.

This study indicates that low dose dopamine significantly attenuates hypoxic ventilatory responses, both when the infusion is started in an already hypoxic subject and when a dopamine-treated subject is made hypoxic. The time course of the depression corresponds to the duration of infusion, reversing after the infusion is terminated. During these experiments, end-tidal gas concentrations were held constant, preventing changes in these variables from affecting ventilation.

In the steady-state hypoxic experiments, end-tidal P_{O_2} was held constant, although we did not measure arterial P_{O_2}. Previous studies (3, 4) indicate that dopamine can widen the alveolar-arterial gradient. We did measure arterial oxygen saturation by ear oximetry and found that in the steady-state hypoxia experiments (Table 1), saturation decreased slightly more than expected after the dopamine infusion was started, but the decrease was not statistically significant. (The average change in $P_{ET O_2}$ from 56.2 to 55.0 torr should cause a decrease in saturation of 1.0% instead of the decrease of 2.2% actually measured.) In the hypoxic step experiments, no change in saturation during dopamine infusion was seen (Table 2). The slight, if any, increase in the alveolar-arterial oxygen tension gradient would tend to counteract the dopamine-induced ventilatory depression.

Dopamine in the dose range we used may increase cardiac output. In five subjects, Horwitz et al (11) found that dopamine (mean dose 8.8 μg/kg/min, range 5.3 to 11.6) increased ventilation by 16.9% (SD = 18.3%) and increased cardiac index by 35% (SD = 21.1%). The increase in cardiac output may itself account for the increase in ventilation by increasing CO_2 flux (12), an effect that would also tend to counter the chemoreceptor depression.

Our results in humans do not localize dopamine's site of action, but it is presumably at the carotid body where the respiratory response to hypoxia is mediated. Animal experiments have shown that dopamine decreases the carotid sinus nerve firing rate (2, 13). However in cats, Nishino and Lahiri (13) found that dopamine caused a decrease in ventilation that could not be explained by a decrease in carotid

chemoreceptor activity. They also found a biphasic depression in minute ventilation even though end-tidal CO_2 was held constant.

We have confirmed the blunting of hypoxic ventilatory drive reported by Welsh et al (5). However, they found that a low dose of dopamine (<5 μg/kg/min) resulted in a biphasic effect during hypoxic-induced hyperpnea (Pa_{O_2} = 40 ± 2.4 torr). There was an initial decrease in ventilation to 58% of control values, but the sustained decrease was 86% of control values. However, in the experiment of Welsh et al it was unclear whether the biphasic response was due to stimulation of excitatory dopamine receptors in the carotid body or was simply due to the stimulation of central chemoreceptors by the increase in CO_2 occurring during hypoventilation. Our experiments have shown that, with end-tidal CO_2 held constant, a biphasic response is not seen. Thus, at least in humans, dopamine does not intrinsically cause a biphasic response.

After the hypoxic steps, the recovery ventilation did not return to control levels (Table 1) in subjects given only saline infusions, a phenomenon that has been observed previously in both man and animals (8, 13). On the basis of animal experiments, this is postulated to be due to activation of a central, long-acting neural mechanism by carotid body afferents (14). It is interesting to note that with the ventilatory response attenuated by dopamine, this effect was not seen.

Ventilatory control in man is quite robust, with respiratory failure primarily arising from lung disease. However, ventilatory control is precarious in certain clinical situations, including morphine administration, myxedema, obesity hypoventilation syndrome, and some hereditary decreases in respiratory drive. A recent case report (15) emphasized the problems associated with morphine administration in a patient with absent carotid body chemosensitivity. Respiratory failure might well ensue if patients who are dependent on hypoxic drive, with a decrease or absence of hypercapnic sensitivity, are treated with dopamine. A warning against the use of dopamine in neonates, who may have depressed central respiratory chemoreflex drive, has been made (16). Whenever dopamine is used in a spontaneously breathing patient, it is imperative to watch for respiratory failure.

ACKNOWLEDGMENTS

The authors wish to thank Kamal Aqleh and Laura Danielson for assistance in performing the experiments and American Critical Care for supplying the dopamine.

REFERENCES

1. Fidone SJ, Cohzalez G, Yoshizaki K. Putative neurotransmitters in the carotid body: the case for dopamine. Fed Proc 1980;39:2636–40.
2. Lahiri S, Nishino T. Inhibitory and excitatory effects of dopamine on carotid chemoreceptors. Neurosci Lett 1980;20:313–8.
3. Mulroy M, Fairley HB. Effect of dopamine on intrapulmonary shunt fraction and oxygen transport in acute pulmonary failure. Am Rev Respir Dis 1977;115:S143.
4. Jardin F, Gurdjian F, Desfonds P, Margairz A. Effect of dopamine on intrapulmonary shunt fraction and oxygen transport in severe sepsis with circulatory and respiratory failure. Crit Care Med 1979;7:273–7.
5. Welsh MM, Heistad DD, Abbound FM. Depression of ventilation by dopamine in man. J Clin Invest 1978;61:708–13.
6. Ward DS, Bellville JW. Effect of dopamine on hypoxic ventilatory drive. Physiologist 1980;23:46.
7. Bradley CA, Fleetham JA, Anthonisen NR. Ventilatory control in patients with hypoxemia due to obstructive lung disease. Am Rev Respir Dis 1979;120:21–30.
8. Swanson GD, Whipp BJ, Kaufman RD, Aqleh KA, Winter B, Bellville JW. Effect of hypercapnia on hypoxic ventilatory drive in carotid body-resected man. J Appl Physiol 1978;45:991–7.
9. Goldberg LI. Cardiovascular and renal actions of dopamine: potential clinical applications. Pharmacol Rev 1972;24:1–29.
10. Goldberg LI. Dopamine-clinical uses of an endogenous catecholamine. N Engl J Med 1974;291:707–10.
11. Horwitz D, Fox S, Goldberg LI. Effects of dopamine in man. Circ Res 1962;10:237–43.
12. Wasserman K, Whipp BJ, Castagna J. Cardiodynamic hyperpnea: hyperpnea secondary to cardiac output increase. J Appl Physiol 1974;36:457–64.
13. Nishino T, Lahiri S. Effects of dopamine on chemoreflexes in breathing. J Appl Physiol 1981;50:893–7.
14. Millhorn DE, Eldridge F, Waldrop TG. Prolonged stimulation of respiration by a new central neural mechanism. Resp Physiol 1980;41:87–103.
15. Lee JK, Hanowell S, Kim YD, Macnamara TE. Morphine-induced respiratory depression following bilateral carotid endarterectomy. Anesth Analg 1981;60:64–5.
16. Kliegman R, Faharoff AA. Dopamine: caution in use in the neonate. J Pediatr 1978;93:540.

ANESTH ANALG
1982;61:338–43

Effects of Sodium Pentobarbital, Ketamine, Halothane, and Chloralose on Brainstem Auditory Evoked Responses

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COHEN, M. S., AND BRITT, R. H.: Effects of sodium pentobarbital, ketamine, halothane, and chloralose on brainstem auditory evoked responses. Anesth Analg 1982;61:338–43.

A parametric study was performed in cats comparing the effects on the brainstem auditory evoked response of four anesthetic agents used either in the operating room or the laboratory: sodium pentobarbital, ketamine, halothane, and chloralose. Each anesthetic agent was administered to each of four cats in varying sequence. Click-evoked brainstem auditory evoked responses (BAER) were compared for differences in wave form configuration, latencies, and amplitudes of the component peaks. Five distinct peaks (I to V) could be identified in the brainstem auditory evoked responses of every animal using each anesthetic agent. There were no statistically significant differences in mean latencies of the component peaks among anesthetic agents. Amplitude differences of the component peaks between animals using the same anesthetic agent were too large to be meaningfully compared. This study suggests that the click-evoked brainstem auditory response is a useful means of monitoring the integrity of the ascending auditory pathway during neurosurgical procedures as the wave form and latencies of the component peaks are not affected by a variety of parenteral and inhalation anesthetic agents.

Key Words: BRAIN: evoked potentials; MONITORING: evoked potentials; ANESTHETICS, Volatile: halothane; ANESTHETICS, Intravenous: pentobarbital, ketamine; PHARMACOLOGY: chloralose.

THE intraoperative use of auditory (1–4), visual (1, 5), and somatosensory evoked potentials (1, 6, 7) is rapidly being adopted to monitor the integrity of these ascending sensory pathways during surgical procedures on the central nervous system. The use of the short latency brainstem auditory evoked response (BAER) has been found particularly useful in monitoring neurosurgical patients in the operating room during posterior fossa surgery for removal of tumors (1, 2, 4) and for procedures involving traction on the cerebellum to expose the fifth and seventh cranial nerves for sectioning or vascular decompression in patients with trigeminal neuralgia or hemifacial spasm (1, 3). The BAER is derived from computer averaging of differentially recorded far-field potentials generated in the nuclei and tracts of the ascending auditory pathway in response to click stimulation (8–13). Seven component waves (I to VII) occurring during the first 10 msec after click stimulation have been identified in the human (14–16). The purpose of the present study was to examine experimentally the effects of four dissimilar anesthetic agents used in the operating room and laboratory on the BAER of the cat to determine whether there are differences in wave form configuration and latencies or amplitudes of the component peaks.

Methods

The effects of four anesthetic agents on the BAER of the cat were evaluated using sodium pentobarbital, ketamine, halothane, and chloralose. Each of four cats was administered all four anesthetics in a varying order with a 1-week recovery period between experimental sessions. Sufficient amounts of drug were administered to induce a surgical level of anesthesia corresponding to stage III, plane ii as defined by Mori,

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Supported by grants from the Veterans Administration (Merit Review: Intracellular and Auditory Evoked Potential Study of the Central Auditory Pathway) and National Institutes of Health NS15860.
Received from the Division of Neurosurgery, Stanford University School of Medicine, Stanford, California, and Palo Alto Veterans Hospital, Palo Alto, California. Accepted for publication December 21, 1981.
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Winter, and Spooner (17). During the recording sessions, respiratory patterns remained constant and the animals displayed no response to noxious stimulation. Induction and maintenance of anesthesia necessarily differed for each anesthetic agent as described below.

Sodium Pentobarbital

Sodium pentobarbital, 40 mg/kg (Nembutal, Abbott Chemical), was administered intraperitoneally. In all cases the cats were sufficiently anesthesized within 5 minutes following the injection. Recording commenced 15 minutes after administration.

Ketamine

A ketamine (Ketalar, Parke-Davis) dosage of 44 mg/kg was injected intramuscularly in the hind limb. Catalepsis lasted 15 to 30 minutes with a single dose. In the event that the total time under anesthesia had to be extended beyond 30 minutes, additional ketamine (22 mg/kg) was given intramuscularly.

Halothane

Halothane (Fluothane, Ayerst Chemical) was administered via a copper kettle. Anesthesia was induced through a tightly fitting face mask. Once gross subject movement ceased, the animal was given 1 mg/kg of succinylcholine intralingually to aid in tracheal intubation. The cats were then ventilated with 0.8% to 1.0% halothane in oxygen (MAC = 1 to 1.25) (18) using a Harvard mechanical respirator with a stroke volume of 50 ml and a rate of 12 breaths per minute. The animals were allowed to equilibrate at this concentration for 30 minutes before recording.

Chloralose

Alpha-chloralose (City Chemical) was prepared in a 50-mg/ml concentration by agitating a solution of 0.5 g of sodium borate, 0.5 g of alpha-chloralose, and 10 ml of sterile saline for 30 minutes at 40°C. This mixture was then filtered under pressure through a sterile Millipore device. Dosages of 70 mg/kg were administered intraperitoneally and 1 hour was allowed before recording was initiated. Fresh solution was made for each experiment.

Temperature was monitored with a rectal probe. The animals were surrounded by a heating jacket and temperature was maintained between 36.5° and 37.5°C, as body temperatures generally tended to decrease slightly during anesthesia.

Following induction of anesthesia the cats were placed in a stereotaxic headholder and alternating polarity clicks (10/sec) were administered through 12.5-cm long hollow earbars using TDH-39 acoustic transducers. Differential recordings between vertex (positive) and mastoid (negative) with reference to ground were made using stainless steel electrodes inserted through the skin. The recordings were amplified 10^6 times, filtered (150 to 3000 Hz, 3-dB down points), and averaged using a Nicolet Med-80 computer system. A total of 500 clicks were averaged for each trial. Clicks were presented binaurally and at intensities from threshold to 90 dB above normal hearing levels for humans. Using the computer the latency and amplitude of each component wave were determined and the wave form was plotted.

Results

The BAER of the cat typically showed five or six distinct component peaks (I to VI) separated in time by approximately 1 msec (Fig 1). The effect of lower intensity acoustic stimulation resulted in increased latency and decreased amplitude of the component peaks using all four anesthetic agents (Fig 1). In the cat wave IV was the dominant component wave peak. With each of the four anesthetic agents all of the five major component peaks were easily identified (Fig 2). The mean latency values for each of the first five peaks are shown in the Table. The standard errors of measurement figures indicate a substantial variability in latency for each of the component peaks. Latency data were tested for intersubject variability using a two-way analysis of variance. Variability between cats for waves II and V was judged significant at the 0.05 level. Wave IV variation was significant at the 0.01 level (F-test). Variability for waves I and III was not significant at the 0.05 level. The average latency for the component peaks of the BAER wave form was: I, 1.75 msec; II, 2.59 msec; III, 3.26 msec; IV, 4.15 msec; and V, 5.50 msec. At 90-dB stimulation intensity it was possible to see wave VI in some animals (Fig 1).

There were no statistically significant differences in mean latencies among the four anesthetic agents used for the five waves (I to V) measured. Amplitudes of the component peaks varied greatly between experimental sessions with the same animal and also between animals using the same anesthetic agent. This suggests that measurement of absolute amplitude at different recording sessions with the same animal or even among animals has little significance in monitoring the effects of anesthesia. The recordings done under ketamine anesthesia were noisier than those with other agents probably because of increased mus-

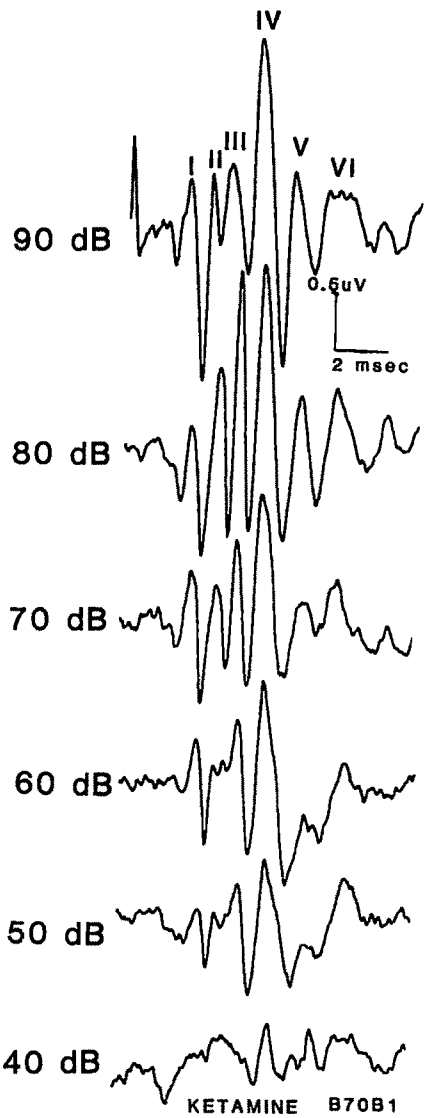


FIG 1. Brainstem auditory evoked responses during ketamine anesthesia as a function of intensity of binaurally presented clicks (dB refers to normal human thresholds to clicks). Note increased latency and decreased amplitude of component peaks I to V as intensity decreases.

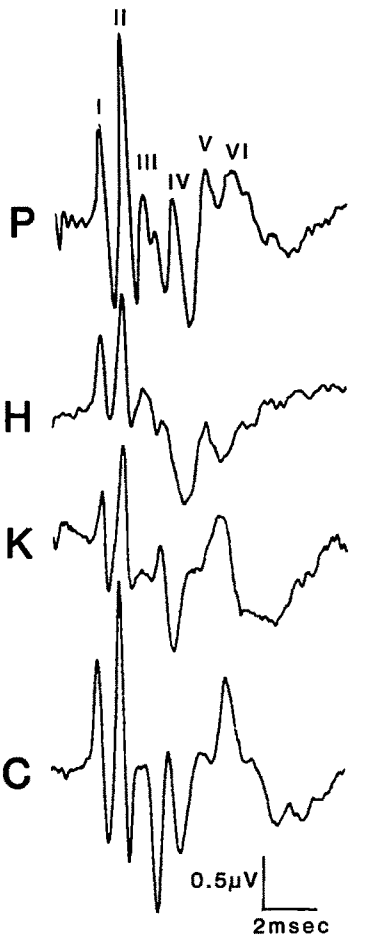


FIG 2. Comparison of BAER tracings under four anesthetic agents [pentobarbital (P), halothane (H), ketamine (K), chloralose (C)] in same cat. Four anesthetic agents were administered at 1-week intervals. Although latencies of component peaks were similar (I to V), there was considerable variation of peak amplitudes. Binaural stimulation was at 90 dB based on normal human hearing threshold.

cle tone remaining with use of this anesthetic agent. The experimental protocol did not permit the differences in latency between anesthetized and unanesthetized animals to be measured. For comparison purposes, however, recordings from cats recovering from halothane anesthesia were used as the "awake" controls (Fig 3, Table). After the halothane administration was stopped, serial BAER recordings were made sequentially until the animal was able to free itself from the stereotaxic holder. The last recording before escape was labeled as the awake tracing. Fig 3 shows BAER recordings from two animals at stage III, plane ii level anesthesia (top tracings) and the bottom tracings present the awake state. Wave VI appears more prominent in the BAER recordings of the near awake condition and the amplitude of wave V is also increased.

Discussion

Opportunities for the anesthesiologist and surgeon to monitor the physiologic state of the central nervous system have greatly increased with the advances in evoked potential technology. Brainstem auditory evoked responses are particularly useful in assessing the structural integrity of the brainstem because of the number of nuclei in the ascending auditory pathway that traverse the length of the brainstem (8–16). Furthermore, the BAER has proven useful in opera-

TABLE

Latencies of Wave Form Peaks (I to V) of Cats' (N = 4) Brainstem Auditory Evoked Responses as Function of Anesthetic Agent*

	I	II	III	IV	V
			msec		
Pentobarbital	1.80 ± 0.31	2.57 ± 0.24	3.33 ± 0.19	4.27 ± 0.19	5.83 ± 0.58
Chloralose	1.72 ± 0.18	2.50 ± 0.13	3.21 ± 0.15	4.12 ± 0.28	5.34 ± 0.44
Ketamine	1.82 ± 0.41	2.78 ± 0.26	3.35 ± 0.31	4.36 ± 0.30	5.68 ± 0.32
Halothane	1.66 ± 0.08	2.51 ± 0.10	3.15 ± 0.30	3.85 ± 0.30	5.15 ± 0.60
"Awake"	1.68 ± 0.07	2.52 ± 0.04	3.31 ± 0.26	4.09 ± 0.42	5.29 ± 0.70

* Values are means ± SEM. Stimulus intensity of binaural clicks was 90 dB per normal human threshold.

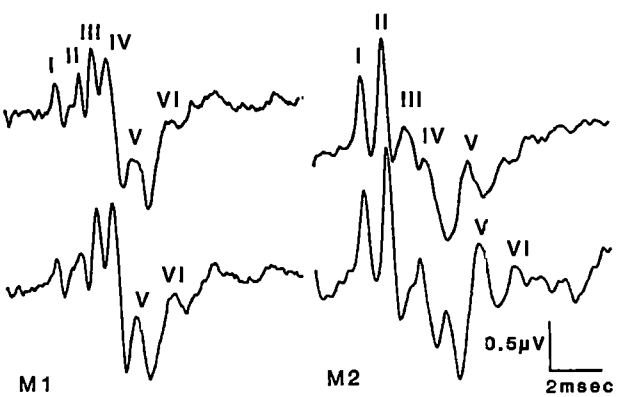


FIG 3. Comparisons of BAER recordings made during level III, plane ii halothane anesthesia (top tracings) and recordings from two cats ("awake" controls) made before the cats freed themselves from stereotaxic holder after cessation of halothane administration (bottom tracings). Note appearance of increased amplitude of wave V and appearance and/or increased amplitude of wave VI. M1 and M2 refer to experimental animal number. Stimulation intensity was 90 dB.

tions commonly performed in the posterior fossa directly involving manipulation of the auditory nerve [e.g., removal of acoustic neuromas or petrous apex meningiomas (1, 2, 4)]. Other surgical procedures, requiring retraction of the cerebellum to expose the fifth cranial nerve (for trigeminal neuralgia) or the seventh cranial nerve (for hemifacial spasm), can involve unintentional stretching of the eighth nerve resulting in permanent hearing loss (1, 3). The use of the BAER has proven useful in the neurosurgical intensive care unit to monitor brainstem function in patients receiving high dose barbiturate therapy for increased intracranial pressure (19).

Of obvious important in using BAER to monitor patients is the effect that anesthetic agents might have on this response. Relatively few studies have addressed this issue. Bobbin and colleagues (20) tested the effect of ketamine and sodium pentobarbital on components I and IV of the BAER in rats. Although both ketamine and pentobarbital significantly decreased heart rate and altered the gross electroencephalographic (EEG) pattern, they did not significantly change the latency or amplitude intensity functions of these two evoked potential components (20). Jewett and Romano (21), in a developmental study of the BAER in both rats and cats, used both halothane and pentobarbital as anesthetic agents. No significant difference in latency was observed in the developmental features of the BAER in a litter of rat pups anesthetized with halothane compared with another litter anesthetized with pentobarbital. They also noted that in older kittens the later waves (V to VI) appeared to have higher amplitudes in higher levels of halothane anesthesia (21). This finding is more completely documented in our study, which demonstrated the relative suppression of wave VI and a lower amplitude of wave V in deep stages of halothane anesthesia.

Recent experiments in our laboratory have demonstrated that the neural origins of waves V and VI come from the inferior colliculus (wave V primarily, waves IV and VI secondarily) and medial geniculate (wave VI primarily) (13). The results of decreased amplitudes of waves V and VI during halothane anesthesia can be explained from a number of reports in which macro- and microelectrode recording studies showed decreased firing rates of neurons and decreased near-field evoked potentials within the inferior colliculus under a wide variety of anesthetic agents including ketamine (22), sodium pentobarbital (23–25), chloralose (23, 24), nitrous oxide (17), and urethane (23, 24).

Aesthesia has been used to study the BAER in uncooperative children. Two studies used halothane and thiopental (25, 26). From halothane concentrations of 0.25% to 2.0% there was no change in the latency or amplitude of wave V in 22 children tested (26). Serial recordings done after injection of thiopental (4 mg/kg) revealed constant amplitudes and latencies of the component peaks (25, 26). Normal appearing wave forms with appropriate latencies have been recorded during surgery using a combination of barbiturates, nitrous oxide, halothane, and pancuronium

bromide (1). A variety of hypnotic and tranquilizing drugs has been used to sedate restless patients for BAER studies, and none has been found to alter the BAER wave form. These drugs include barbiturates (27–29), chloral hydrate (30, 31), diazepam (29, 32), and paraldehyde (29). In contrast to the BAER, the middle latency (33, 34) and long latency auditory evoked responses (35–39), representing activity at levels above the inferior colliculus, are markedly affected by anesthetic agents.

It is important for both the anesthesiologist and surgeon to understand which physiologic parameters will affect the wave form configuration and latencies of the component peaks of the BAER during surgery. The effects of temperature (40), mean arterial pressure (MAP), and arterial pH on the BAER have been studied in our laboratory during acute experiments on pentobarbital-anesthetized cats. Cats were placed on cardiopulmonary bypass (41) and the brain temperature was systematically decreased from 37° to 19°C using the heat exchanger. The latency of waves I to V linearly increased as the temperature was decreased to 26°C, but the wave form configuration did not change. The latency of the early components (I to III) increased less than that of the late waves (IV to V) (40). For example, the latency of wave I increased 0.7 msec when the temperature decreased from 37° to 26°C, but the latency of wave V increased 4.5 msec (40). As temperature often falls during general anesthesia the individual monitoring the evoked potentials must record esophageal temperature accurately and interpret the results of the BAER based on these temperature-dependent effects.

The chronic nature of the experiments reported in this paper did not easily permit invasive monitoring of mean arterial pressure or arterial blood gases. However, using the same anesthetic dose of sodium pentobarbital, a series of acute experiments was performed using cats in which both a continuous record of MAP and frequent sampling of arterial blood gases (pH, P_{O_2}, P_{CO_2}) were obtained (41). Mean arterial pressure ranged from 90 to 160 mm Hg. Arterial blood gas tensions were within the normal range for the awake cat (42). The effect of MAP on the BAER was studied by systematically lowering the pressure using a trimethaphan camsylate (Arfonad, Roche Laboratories) infusion. The BAER wave form was not affected until the MAP was decreased to less than 40 mm Hg. Further reduction in pressure resulted in drastic reductions in amplitude and eventual loss of the component waves beginning with wave V and ending with only wave I remaining (41) and indicated inadequate perfusion of the brainstem. Similar changes could be expected to occur during prolonged hypotension during neurosurgical procedures.

In experimental studies in the pentobarbital-anesthetized cat, changes in the arterial pH using different ventilatory parameters did not affect the BAER (43). Metabolic acidosis (pH 7 to 7.2) also is not associated with any changes of the BAER (41). During surgical monitoring of evoked potentials, changes in acid-base balance should not alter the BAER.

This study confirms and extends the findings of other investigators that the basic wave form of the BAER is unchanged after exposure to a variety of parenteral and inhalation anesthetic agents. Although the amplitudes may vary greatly between anesthetic agents or at different recording sessions with the same anesthetic agent, the latencies of the component peaks are not altered for waves I to V. However, even under general anesthesia, the relative amplitude of the response at a given recording session may still be useful for monitoring potentially important physiologic changes attendant to the course of an operative procedure. There is little doubt that the use of the brainstem auditory evoked response will be increasingly utilized to monitor the function of the auditory pathway specifically, but also more generally as a measure of brainstem structural integrity and function.

ACKNOWLEDGMENTS

The authors thank Ellis Cohen, MD, Professor of Anesthesia, for aiding these experiments and Cindy Hollman for manuscript preparation.

REFERENCES

1. Allen A, Nudleman K, Starr A. Assessment of sensory function in the operating room utilizing cerebral evoked potentials: a study of fifty-six surgical anesthesized patients. Clin Neurosurg (in press 1981).
2. Hashimoto I, Ishiyama Y, Totsuka G, Mizhtani H. Monitoring brainstem function during posterior fossa surgery with brainstem auditory evoked potentials. In: Barber C, ed. Evoked potentials. Cambridge, MA: MIT Press, 1980.
3. Grundy BL, Lina A, Procopio PT, Jannetta PJ. Reversible evoked potential changes with retraction of the eighth cranial nerve. Anesth Analg 1981;60:835–8.
4. Levine RA, Montgomery WW, Ojemann RG, Springer MEB. Evoked potential detection of hearing loss during acoustic neuroma surgery. Neurology 1978;28:339.
5. Uhl RR, Squires KC, Bruce DL, Starr A. Effect of halothane anesthesia on human cortical visual evoked response. Anesthesiology 1980;53:273–6.
6. Engler GL, Spielholz NI, Bernhard WN, Danzier F, et al. Somatosensory evoked potentials during Harrington instrumentation for scoliosis. J Bone Joint Surg 1978;60A:528–32.
7. Hall JE, Levine CR, Sudhir KG. Intraoperative awakening to monitor spinal cord function during Harrington instrumentation and spine fusion. J Bone Joint Surg 1978;60A:533–6.

8. Jewett DL. Volume-conducted potentials in response to auditory stimuli as detected by averaging in the cat. Electroencephalogr Clin Neurophysiol 1970;28:609–18.
9. Buchwald JS, Huang CM. Far-field acoustic response: origins in the cat. Science 1975;189:382–4.
10. Achor LJ, Starr A. Auditory brain stem responses in the cat. I. Intracranial and extracranial recordings. Electroencephalogr Clin Neurophysiol 1980;48:154–73.
11. Achor LJ, Starr A. Auditory brain stem responses in the cat. II. Effects of lesions. Electroencephalogr Clin Neurophysiol 1980;48:174–90.
12. Britt R, Rossi G. Neural generators of brainstem auditory evoked responses. Part I. Lesion studies (abstract). Neuroscience 1980;6:594.
13. Rossi G, Britt R. Neural generators of brainstem auditory evoked responses. Part II. Electrode recording studies (abstract). Neuroscience 1980;6:595.
14. Jewett DL, Williston JS. Auditory-evoked far field averaged from the scalp of humans. Brain 1971;94:681–96.
15. Picton TW, Hillyard SA, Krausz HI, Galambos R. Human auditory evoked potentials. I. Evaluation of components. Electronencephalogr Clin Neurophysiol 1974;36:179–90.
16. Chiappa KH, Gladstone KJ, Young RR. Brain stem auditory evoked responses: studies of waveform variations in 50 normal human subjects. Arch Neurol 1979;36:81–7.
17. Mori K, Winters WD, Spooner CE. Comparison of reticular and cochlear multiple unit activity with auditory evoked responses during various stages induced by anesthetic agents. Electroencephalogr Clin Neurophysiol 1968;24:242–8.
18. Brown BR Jr, Crout JR. A comparative study of the effects of five general anesthetics on myocardial contractility. I. Isometric conditions. Anesthesiology 1971;34:236–45.
19. Rockoff, MA, Marshall LF, Shapiro HM. High-dose barbiturate therapy in human: a clinical review of 60 patients. Ann Neurol 1979;6:194–9.
20. Bobbin RP, May JG, Lemoine RL. Effects of pentobarbital and ketamine on brain stem auditory potentials: latency and amplitude intensity functions after intraperitoneal administration. Arch Otolaryngol 1979;105:467–70.
21. Jewett DL, Romano MN. Neonatal development of auditory system potentials averaged from the scalp of the rat and cat. Brain Res 1972;36:101–15.
22. Dafny N, Rigor BM. Dose effects of ketamine on photic and acoustic field potentials. Neuropharmacology 1978;17:851–62.
23. Nakai Y, Takaori S, Shimamoto K. Effects of central depressants on the evoked potentials in the inferior colliculus caused by acoustic stimuli in the cat. Jpn J Pharmacol 1965;15:201–9.
24. Nakai Y, Matsuoka I, Takaori S. Pharmacological analysis of unitary discharges recorded from the inferior colliculus of cats. Jpn J Pharmacol 1965;15:378–85.
25. Walker JR, Teas DC. The effect of small concentrations of sodium pentobarbital on auditory evoked responses. J Aud Res 1974;14:73–81.
26. Duncan PG, Sanders RA, McCullough DW. Preservation of auditory-evoked brainstem responses in anaesthetized children. Can Anaesth Soc J 1979;26:492–5.
27. Sanders RA, Duncan PG, McCullough DW. Clinical experience with brainstem auditometry performed under general anesthesia. J Otolaryngol 1979;8:24–32.
28. Goff WR, Allison T, Lyons W, Fisher TE, et al. Origins of short latency auditory evoked potentials in man (auditory evoked potentials in man—psychopharmacology correlates of evoked potentials). Prog Clin Neurophysiol 1977;2:30–44.
29. Davis H, Hirsh SK. The audiometric utility of brain stem responses to low-frequency sounds. Audiology 1976;15:181–95.
30. Sohmer H, Student M. Auditory nerve and brain stem evoked responses in normal, autistic, minimal brain dysfunction and psychomotor retarded children. Electroencephalogr Clin Neurophysiol 1978;44:380–8.
31. Mokotoff B, Schulman-Galambos C, Galambos R. Brainstem auditory evoked responses in children. Arch Otolaryngol 1977;103:38–43.
32. Stockard JJ, Rossiter VS. Clinical and pathologic correlates of brain stem auditory response abnormalities. Neurology 1977;27:316–25.
33. Starr A, Achor LJ. Auditory brain stem responses in neurological disease. Arch Neurol 1975;32:761–8.
34. Mendel ME, Hosick EC. Effects of secobarbital on the early components of the auditory evoked potentials. Rev Laryngol Otol Rhinol 1975;96:178–84.
35. Skinner P, Shimota J. A comparison of the effects of sedatives on the auditory evoked cortical response. J Am Aud Soc 1975;1:71–8.
36. Hosick EC, Mendel MI. Effects of secobarbital on the late components of the auditory evoked potentials. Rev Laryngol Otol Rhinol 1975;96:185–91.
37. Kiang NY-S, Neame JH, Clark LF. Evoked cortical activity from auditory cortex in anesthetized and unanesthetized cats. Science 1961;133:1927–8.
38. Pradhan SN, Galambos R. Some effects of anesthetics on the evoked responses in the auditory cortex of cats. J Pharmacol Exp Ther 1963;139:99–106.
39. Rabe LS, Moreno L, Rigor BM, Dafny N. Effects of halothane on evoked field potentials recorded from cortical and subcortical nuclei. Neuropharmacology 1980;19:813–25.
40. Rossi GT, Britt RH. Hypothermia effects on cat brainstem auditory evoked responses (abstract). Neuroscience 1981;7:282.
41. Britt RH, Rossi GT. Quantitative study of brainstem movement and methods which may be used to reduce it: develoment of a nonpulsatile cardiopulmonary perfusion system for the cat (abstract). Neuroscience 1981;7:54.
42. Herbert DA, Mitchell RA. Blood gas tensions and acid-base balance in awake cats. J Appl Physiol 1971;30:434–6.
43. Raudzens P, Scharber R, Erpsamer R. Intracranial pressure effects on brainstem potentials. Anesthesiology 1979;51:S40.

ANESTH ANALG
1982;61:344-8

Anesthesia and the Control of Blood Pressure in Patients with Spinal Cord Injury

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LAMBERT, D. H., DEANE, R. S., AND MAZUZAN, J. E., JR.: Anesthesia and the control of blood pressure in patients with spinal cord injury. Anesth Analg 1982;61:344-8.

The medical records of 78 procedures performed on 50 spinal cord injured patients at risk for developing autonomic hyperreflexia were evaluated for blood pressure changes during anesthesia and surgery. Hypertension was arbitrarily defined as a systolic blood pressure of greater than 140 torr. The 78 procedures were divided into three groups: group A, 19 procedures in which the patient received topical anesthesia, sedation, or no anesthesia; group B, 13 procedures conducted under general anesthesia; and group C, 46 procedures carried out under spinal anesthesia. Hypertension occurred in 15 of 19 procedures (79%) in group A, in three of 13 procedures (23%) in group B, and in three of 46 procedures (7%) in group C. Group A differed significantly from group B ($p = 0.011$) and group C ($p = 1.2 \times 10^{-8}$). There was no significant difference between groups B and C ($p = 0.114$). Results indicate that patients at risk for autonomic hyperreflexia are protected from developing intraoperative hypertension by either general or spinal anesthesia.

Key Words: SPINAL CORD: injuries; COMPLICATIONS: spinal cord injury.

IN THE spinal cord injured patient with a lesion above T-7 hypertension resulting from autonomic hyperreflexia during surgery performed below the level of the spinal cord lesion occurs in 65% to 85% of patients (1-4). Presently, there is no agreement among anesthesiologists on the management of patients at risk for developing autonomic hyperreflexia (5). Topical anesthesia, alpha adrenergic antagonists, ganglioplegics, sodium nitroprusside, inhalation anesthesia, epidural anesthesia, and spinal anesthesia have all been advocated and used with varying success (5-15). Broecker et al (15) suggest that spinal anesthesia, by blocking the afferent limb of this potentially lethal reflex, is a logical choice of anesthesia for prevention of autonomic hyperreflexia. However, spinal anesthesia in the patient with spinal cord injury has been said to be difficult to perform and difficult to control; it may be ineffective, or it may lead to hypotension because of circulatory instability (3, 16). The present retrospective study was undertaken to quantitate the effectiveness of spinal, general, and other types of anesthesia on blood pressure during surgery in the patient with spinal cord injury.

Methods

The medical records of 88 patients with spinal cord injury treated at the Medical Center Hospital of Vermont between December 1969 and April 1981 were reviewed. In particular, the anesthesia records of patients with lesions at or above T-7, considered to be "at risk" for developing autonomic hyperreflexia (1), were examined. Our goal was to evaluate hypertension that resulted from autonomic hyperreflexia. Therefore, only anesthesia records for procedures performed below the lesion were included in the study. Procedures performed at or above the lesion were excluded. In this manner, hypertension resulting from surgical stimulation of areas not rendered anesthetic as a result of the spinal cord injury was eliminated. Preanesthesic systolic blood pressures were noted and intraoperative systolic blood pressures were evaluated. In extracting the data from the anesthetic records, the highest systolic blood pressure

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Received from the Section of Anesthesiology, Department of Surgery, University of Vermont, College of Medicine, Burlington, Vermont. Accepted for publication December 21, 1981.
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was noted if the intraoperative systolic blood pressure never decreased to less than 100 torr. When the systolic blood pressure never exceeded 140 torr but pressures less than 100 torr were obtained, the lowest systolic blood pressure was noted. In cases in which there were systolic blood pressures greater than 140 torr and less than 100 torr, the maximum intraoperative systolic blood pressure was noted.

Operative procedures were divided into three groups: group A included procedures performed with topical anesthesia, sedation, or no anesthesia; group B procedures were performed under general anesthesia; and group C procedures were done under spinal anesthesia.

Statistical significance between preanesthesic and intraoperative systolic blood pressures was compared within each group by the standard paired *t*-test and between the groups by the standard nonpaired *t*-test. Statistical significance of differences between anesthetic techniques was assessed by calculating exact probabilities for enumeration data. A probability less than 0.05 was considered a statistically significant difference.

Results

Distribution of the patient population and numbers of operations studied are shown in Fig 1. Of the 88 records evaluated, the level of the spinal cord lesion was above T-7 in 67 and below T-7 in 21. A total of 139 procedures were performed on the 67 patients with lesions above T-7. Of the 139 procedures 61 were excluded from the study. In 15 of these procedures, the blood pressure data were inadequate for analysis and in 46 the procedures were performed at or above the lesion. The remaining 78 procedures, performed below the lesion, were carried out in 50 patients.

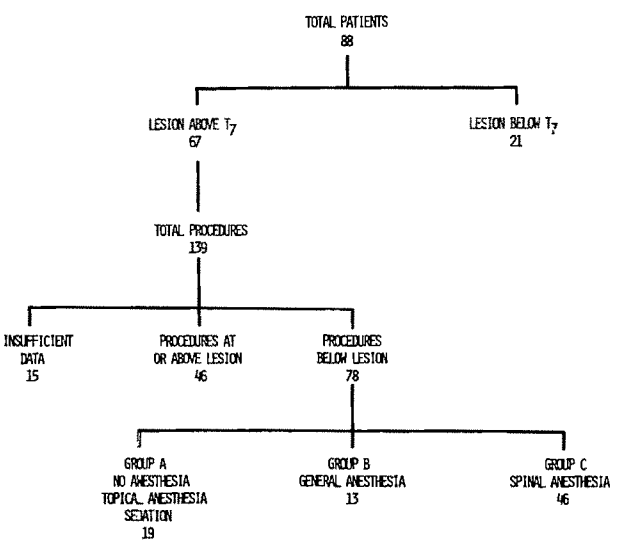


FIG 1. Distribution of patient population and numbers of procedures studied.

The majority of the procedures were urologic, consisting mostly of cystoscopies and litholapaxies. However, there were also a number of plastic procedures done for decubitus ulcers as well as orthopedic procedures done for contractures. In group A, eight procedures were done with sedation with diazepam, fentanyl, alphaprodine, pentobarbital, or some combination thereof; two procedures were done with lidocaine topically; and nine procedures were done with no anesthesia. In group B, seven procedures were done with halothane/O_2, three with halothane/N_2O/O_2, one with enflurane/O_2, one with morphine/O_2, and one with Innovar/N_2O/O_2/relaxant. Of the 46 procedures performed in group C, 21 were performed with lidocaine (mode = 50 mg, range = 30 to 70 mg) and 25 were performed with tetracaine (mode = 10 mg, range = 6 to 13 mg).

The Table shows the mean preanesthetic and intraoperative systolic blood pressures. When compared with the preanesthetic systolic blood pressure, the intraoperative systolic blood pressure was significantly higher in group A ($p < 0.005$), not significantly different in group B ($p < 0.8$), and significantly lower in group C ($p < 0.001$). The preanesthetic systolic blood pressures in group A were significantly higher than those in group B ($p < 0.001$) and group C ($p < 0.005$). There was no significant difference in the preanesthetic systolic blood pressures between groups B and C ($p < 0.3$).

Fig 2, a graphic representation of the data, shows the spread of the intraoperative systolic blood pres-

TABLE

Preanesthetic and Intraoperative Systolic Blood Pressures*

Group	Anesthetic technique	Preanesthesia systolic blood pressure	Intraoperative systolic blood pressure	*p*
		torr		
A	Topical anesthesia, sedation, or no anesthesia	135 ± 20	172 ± 44	<0.005
B	General anesthesia	110 ± 13	107 ± 34	<0.8
C	Spinal anesthesia	117 ± 19	103 ± 21	<0.001

* Values are means ± SD. Preanesthesic systolic blood pressures: A vs B, $p < 0.001$; A vs C, $p < 0.005$; B vs C, $p < 0.3$. Intraoperative systolic blood pressures: A vs B, $p < 0.001$; A vs C, $p < 0.001$; B vs C, $p < 0.7$.

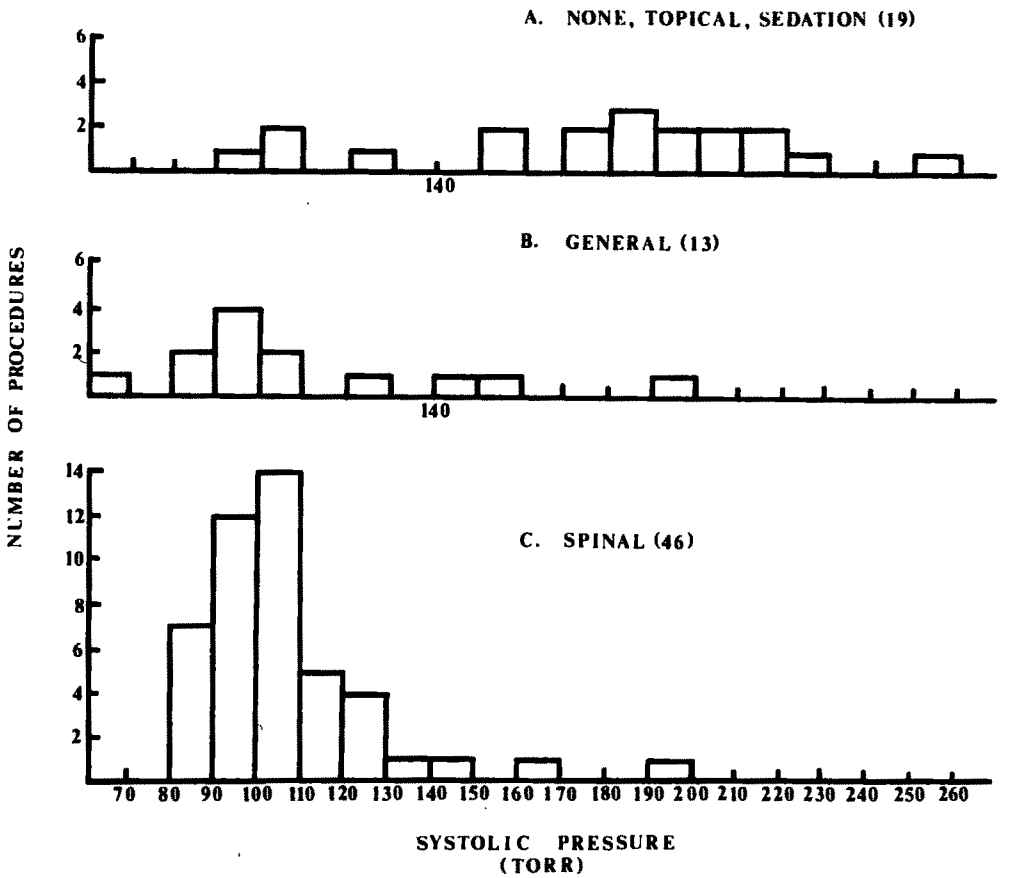


FIG 2. Distribution of intraoperative systolic blood pressures in multiples of 10 torr and number of procedures in which these individual blood pressures were observed. Group A received topical anesthesia, sedation, or no anesthesia; group B received general anesthesia; and group C received spinal anesthesia.

sures in multiples of 10 torr and the number of procedures demonstrating these individual pressures. In group A hypertension developed in 15 of 19 procedures (79%). Of those procedures resulting in hypertension, one was done with topical anesthesia, five with diazepam for sedation, one with a combination of drugs for sedation, and eight with no anesthesia. In group B three of 13 procedures (23%) resulted in hypertension. One of these was performed with enflurane/O_2, one with Innovar/N_2O/O_2/relaxant, and the other with morphine/O_2. In group C three of 46 procedures (7%) resulted in hypertension. Two of these were done with 12 mg of tetracaine and one with 6 mg of tetracaine. Group A differed significantly from group B ($p = 0.011$) and group C ($p = 1.2 \times 10^{-8}$). However, there was no significant difference between groups B and C ($p = 0.114$).

Six of the patients who became hypertensive in group A had on other occasions received general anesthesia (four patients, nine anesthetics) or spinal anesthesia (five patients, thirteen anesthetics). Only one of these patients developed intraoperative hypertension once with spinal anesthesia. This particular patient developed hypertension on two occasions when he received no anesthesia, was normotensive during two general anesthetics, and was hypertensive during one of three spinal anesthetics. This demonstrates the value of general or spinal anesthesia in the patient at risk for autonomic hyperreflexia.

Discussion

This study shows that general or spinal anesthesia is necessary to control hypertension during surgery in the spinal cord injured patient at risk for developing autonomic hyperreflexia. Furthermore, the suggestion that spinal anesthesia may be difficult to perform, difficult to control, ineffective, or cause hypotension (3, 16) in these patients is not substantiated by our data. Although intraoperative systolic blood pressures in our patients given spinal anesthesia were lower than preanesthetic systolic blood pressures, there was

no difference in intraoperative blood pressures between patients who received general anesthesia and those given spinal anesthesia (Table). This indicates that in this type of patient spinal anesthesia is no more likely to result in hypotension than general anesthesia.

Patients who received topical anesthesia, sedation, or no anesthesia had higher preoperative blood pressures than patients given general or spinal anesthesia. We are uncertain why this should be. Two possibilities come to mind. First, it is possible that this is due to bias in reporting—a well known drawback to retrospective studies such as this. Second, the elevated preoperative blood pressures may be due either to anxiety associated with being informed that surgery would be performed without anesthesia or to anxiety resulting from lack of preoperative medication. Of the 19 procedures performed in group A, 10 were done without premedication whereas in group B all procedures but one were done with premedication. In group A the preoperative blood pressures prior to procedures done with premedication were an average of 10 torr lower than those done without premedication. This difference was not statistically significant. It is justifiable to ask whether or not premedication of group A would have prevented intraoperative hypertension. If premedication is a determinant in prevention of intraoperative hypertension, then all premedicated patients should be protected. Of the nine procedures in group A done with premedication, seven resulted in hypertension. Furthermore, all but one procedure resulting in intraoperative hypertension in groups B and C were done with premedication. It is unlikely, therefore, that lack of premedication can account for the significantly higher number of patients who developed intraoperative hypertension in group A.

It has been suggested that topical anesthesia for cystoscopy is a satisfactory means of preventing autonomic hyperreflexia (5). Because only two of our patients were given topical anesthesia, no conclusions can be drawn. One of these patients became hypertensive during surgery. During cystoscopy, topical anesthesia, in theory, should not block bladder stretch receptors and reflex hypertension might be expected.

In regard to general anesthesia, our results are in agreement with those reported by Drinker and Helrich (10) and by Alderson and Thomas (11) that halothane effectively controls autonomic hyperreflexia. None of our patients given halothane became hypertensive. The three patients receiving general anesthesia who became hypertensive received enflurane, Innovar/N_2O/O_2/relaxant, or morphine anesthesia. It may be that the greater incidence of hypertension associated with enflurane and N_2O-narcotic anesthesia was due to anesthetic depth. The depth of anesthesia produced with enflurane or N_2O-narcotic anesthesia may not have been as adequate as that produced by halothane. However, the sample size is again too small to draw conclusions.

Many anesthesiologists elect inhalation anesthesia instead of spinal anesthesia when autonomic hyperreflexia may be a problem because they feel that with spinal anesthesia the level is difficult to control and hypotension may result (3). Circulatory depression, however, is common with inhalation anesthesia. It is often necessary to provide deep inhalation anesthesia to prevent or treat autonomic hyperreflexia. Under these circumstances it is usually advantageous to control ventilation, especially in these patients with diminished pulmonary reserves. The combination of deep inhalation anesthesia and inhibition of venous return resulting from positive pressure ventilation makes hypotension as likely to occur under these circumstances as with spinal anesthesia. Although a few patients given general or spinal anesthesia had intraoperative systolic blood pressures less than 100 torr, the mean blood pressures in each group were close to 100 torr and they were not significantly different (Fig 2, Table). It seems, therefore, that although hypotension is a possible complication of either general or spinal anesthesia it does not appear to be a major problem.

None of our patients received alpha adrenergic antagonists, ganglioplegics, sodium nitroprusside, or epidural anesthesia. A ganglionic blocking agent that has been widely used is pentolinium (9). Although effective, pentolinium is no longer available. Sodium nitroprusside has been suggested for the rapid control of hypertension due to autonomic hyperreflexia (6). Most would agree that prolonged administration of sodium nitroprusside requires insertion of an arterial catheter for continuous monitoring of arterial pressure. Ravindran et al (17) reported that they were unable to control blood pressure with sodium nitroprusside in a quadriplegic parturient in labor but gained control of systemic pressure when epidural anesthesia was instituted. A few reports (13, 17) suggest that epidural anesthesia may be especially useful for prolonged labor and delivery in patients at risk for development of autonomic hyperreflexia. On the other hand, Broecker et al (15) found epidural anes-

thesia ineffective in preventing hypertension during urologic endoscopic procedures in patients with spinal cord injury. This could perhaps be predicted as epidural anesthesia may not always provide adequate sacral anesthesia (18).

It has become our policy to elect low spinal anesthesia in patients at risk for autonomic hyperreflexia unless there are contraindications. The data presented here support our belief that interrupting the afferent loop of the autonomic hyperreflexia reflex arc with low spinal anesthesia is logical, effective, easily performed, easily controlled, and causes little or no morbidity. For most procedures, sacral anesthesia is adequate and the amount of anesthetic agent required is small (15).

ACKNOWLEDGMENTS

We thank Drs. H. Lawrence McCrorey and T. Shinozaki for aid with the statistical analyses.

REFERENCES

1. Kendrick WW, Scott JW, Jousse AT, Botterell EH: Reflex sweating and hypertension in traumatic transverse myelitis. Treat Servs Bull Can 1953;8:437–48.
2. Bors E: The challenges of quadriplegia: some personal observations in series of 233 cases. Bull Los Angeles Neurol Soc 1956;2:105–23.
3. Desmond J: Paraplegia: problems confronting the anaesthesiologist. Can Anaesth Soc J 1970;17:435–51.
4. Kurnick NB: Autonomic hyperreflexia and its control in patients with spinal cord lesions. Ann Intern Med 1956;44:678–86.
5. Rao MS, Bapna BC, Vaidyanathan, et al: Topical or no anesthesia for external urethral sphincterectomy in neurogenic vesical dysfunction due to spinal injury. Paraplegia 1977;15: 226–9.
6. Vandam LD, Rossier AD: Circulatory, respiratory and ancillary problems in acute and chronic spinal cord injury. In: Hershey SG, Bridenbaugh PO, Carnes MA, Bamforth FJ, eds. ASA refresher courses in anesthesiology. Philadelphia: Lippincott, vol 3, 1975:171–82.
7. Johnson B, Thomason R, Pallares V, Sadove MS: Autonomic hyperreflexia: a review. Milit Med 1975;140:345–9.
8. Rocco AG, Vandam LD: Problems in anesthesia for paraplegics. Anesthesiology 1959;20:348–54.
9. Texter JH, Reece RW, Hranowsky EA: Pentolinium in the management of autonomic hyperreflexia. J Urol 1976;116:350–1.
10. Drinker AS, Helrich M: Halothane anesthesia in the paraplegic patient. Anesthesiology 1963;24:399–400.
11. Alderson JD, Thomas DG: The use of halothane anaesthesia to control autonomic hyperreflexia during trans-urethral surgery in spinal cord injury patients. Paraplegia 1975;13:183–8.
12. Nieder RM, O'Higgins JW, Aldrete JA: Autonomic hyperreflexia in urologic surgery. JAMA 1970;213:867–9.
13. Stirt JA, Marco A, Conklin KA: Obstetric anesthesia for a quadriplegic patient with autonomic hyperreflexia. Anesthesiology 1979;51:560–2.
14. Ciliberti BJ, Goldfein J, Rovenstine EA. Hypertension during anesthesia in patients with spinal cord injuries. Anesthesiology 1954;15:273–9.
15. Broecker BH, Hranowsky N, Hackler RH. Low spinal anesthesia for the prevention of autonomic dysreflexia in the spinal cord injury patient. J Urol 1979;122:366.
16. Katz J, Benumof J, Kadis LB: Anesthesia and uncommon diseases. Philadelphia: WB Saunders, 1981:650–1.
17. Ravindran RS, Cummins DF, Smith IE: Experience with the use of nitroprusside and subsequent epidural analgesia in a pregnant quadriplegic patient. Anesth Analg 1981;60:61–3.
18. Galindo A, Hernandez J, Benavides O, Ortegon De Munoz S, Bonica JJ: Quality of spinal extradural anaesthesia: the influence of spinal nerve root diameter. Br J Anaesth 1975;47:41–7.

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1982;61:349-53

Hemodynamic and Catecholamine Changes after Administration of Naloxone

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ESTILO, A. E., AND COTTRELL, J. E.: Hemodynamic and catecholamine changes after administration of naloxone. Anesth Analg 1982;61:349-53

The hemodynamic and catecholamine response to intravenously administered naloxone, 0.2 mg and 0.4 mg, were determined in one group of surgical patients and one group of volunteers. Naloxone, 0.2 mg, was administered 30 minutes before the 0.4-mg dose. Group I consisted of six normotensive (IA) (aged 18 to 64, mean 35.7 years) and six hypertensive surgical patients (IB) (aged 35 to 67, mean 49.1 years) who were receiving a nitrous oxide, oxygen, and halothane anesthetic. Group II consisted of six normotensive (IIA) (aged 27 to 38, mean 36.1 years) and five hypertensive (IIB) unanesthetized volunteers (aged 41 to 60, mean 51.4 years). Mean arterial pressure, heart rate, plasma norepinephrine, epinephrine, and dopamine levels were compared before and after intravenous naloxone. Changes in mean arterial pressure, heart rate, plasma norepinephrine, epinephrine, and dopamine levels were not statistically significant in any group. This study suggests that intravenous naloxone, per se, alters neither mean arterial pressure, heart rate, or plasma catecholamine levels in normotensive or hypertensive humans.

Key Words: ANTAGONISTS, Narcotic: naloxone; SYMPATHETIC NERVOUS SYSTEM: catecholamine blood levels.

NALOXONE is a potent and specific narcotic antagonist. It had previously been considered a safe drug until side effects such as severe hypertension, pulmonary edema, ventricular irritability, and cardiac arrest were reported following its administration intravenously for narcotic reversal (1-5). Desmonts et al (6) found that even small doses of naloxone (1.5 μg/kg) given intravenously to reverse narcotic effects is followed immediately by marked increases in heart rate, blood pressure, and cardiac output. We previously observed severe hypertension (260/140 torr) and subsequent aneurysm rupture after 0.4 mg of IV naloxone for reversal of fentanyl-induced respiratory depression (7). Naloxone has also been reported to reverse the early hypotension of endotoxin shock (8) and to improve the hypotension observed after cervical spinal cord injury (9). To determine the relation between IV naloxone and these hemodynamic responses we measured plasma norepinephrine (NE), epinephrine (E), and dopamine (DA) levels in normotensive and hypertensive surgical patients and unanesthetized volunteers before and after IV naloxone.

Methods and Materials

Informed consent from patients and volunteers and approval by the Hospital's Health Sciences Review Committee on Investigations Involving Human Subjects were previously obtained.

Intravenous and arterial catheters were placed in all patients and volunteers for fluid and drug administration and for blood sampling for measurement of arterial blood gas tensions and plasma levels of NE, E, and DA. Systemic blood pressure and heart rate and rhythm were continuously monitored via oscilloscope, a Statham P50 transducer, and a Tektronix 414 monitor with a continuous recorder. Temperature was monitored via esophageal temperature probe only in anesthetized patients. Antihypertensive medications were discontinued 12 hours before the study.

All 12 surgical patients, A.S.A. physical status I to II, were premedicated with oral diazepam, 0.1 mg/kg, 90 minutes before the scheduled general surgical operation. Normotensive patients (group IA) included those scheduled for plastic surgical procedures. Hypertensive patients (group IB) included four patients scheduled for gynecologic operations and two patients scheduled for orthopedic procedures. Thiopental, 3 to

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5 mg/kg, was administered intravenously as necessary to produce sleep, and succinylcholine, 1.0 mg/kg, was administered intravenously to aid endotracheal intubation. Anesthesia was maintained in groups IA and IB with inspired halothane concentrations as needed in conjunction with 60% N_2O in oxygen. If muscle relaxation was necessary pancuronium bromide, 0.04 mg/kg, was administered intravenously. All blood samples for NE, E, and DA measurement were collected in ice-cooled heparinized syringes and centrifuged for 10 minuts. The plasma was transferred in cooled plastic tubes and frozen until radio enzymatic laboratory assay (10, 11) for NE, E, and DA was performed. Control samples were taken in groups IA and IB after anesthetic stabilization with halothane for at least 1 hour and when surgical stimulation was at a minimum. Eleven volunteers included six normotensive healthy subjects (group IIA) and five hypertensives, with no other known disease (group IIB). They did not receive premedication and were not anesthetized. Control samples were taken in groups IIA and IIB 1 hour after placement of monitors and catheters. Intravenous naloxone, 0.2 mg, was then administered to patients in groups IA and IB and to subjects in groups IIA and IIB. After 30 minutes, IV naloxone, 0.4 mg, was again administered. Blood samples were taken 5 minutes after each dose for measurement of plasma levels of NE, E, and DA and for measurement of arterial blood gas tensions. Statistical analysis was performed using Student's *t*-test for paired data and significance defined as p equal to or less than 0.05.

Results

The duration of anesthesia and surgery was 212 ± 32 minutes for the normotensive patients and 180 ± 26 minutes for the hypertensive patients.

No significant change in blood pressure or heart rate was noted at any observation period following IV naloxone, 0.2 mg and 0.4 mg, in normotensive or hypertensive patients anesthetized with halothane. Mean plasma levels of NE and DA increased after IV naloxone, 0.2 and 0.4 mg, but these changes were not statistically significant (Tables 1 and 2). Mean plasma levels of E also increased after 0.2 mg but decreased slightly after 0.4 mg of naloxone (Table 2). The changes, although noticeable, were not statistically significant.

Blood pressure and heart rate did not change significantly after 0.2 mg and 0.4 mg of IV naloxone in the normotensive or hypertensive unanesthetized volunteers (Tables 3 and 4). The mean levels of DA for the hypertensive volunteers were higher than the normal range (undetectable to 90 pg/ml) and the standard errors were high. Plasma levels of DA did not consistently increase following administration of IV naloxone as mean DA decreased with 0.2 mg and increased after 0.4 mg.

Discussion

The hypertension and arrhythmia that were previously reported occurred following naloxone reversal of narcotics. Recovery from general anesthesia by itself is associated with increased autonomic nervous system discharge (6), the pattern being dependent upon the anesthetic and adjuvant drugs that may have been used. In patients without heart disease this is manifested by increases in heart rate, arterial pressure, cardiac output, and systemic vascular resistance. As naloxone administered after opiates reverses not only the respiratory depressant effects of narcotics but also its analgesic and sedative effects, the rapid awakening and perception of pain were considered as possible causes of the hypertensive response. Patschke et al (12) anesthetized dogs with halothane and nitrous oxide and subsequently gave intravenous morphine followed by a reversal dose of naloxone, while anesthesia was maintained, and observed a significant increase in systemic blood pressure. This finding contradicts the view that reversal of analgesia is the cause of the hypertensive response. They did not, however, measure plasma levels of catecholamines.

TABLE 1

Mean Arterial Pressure (MAP), Heart Rate (HR), and Plasma Levels of Dopamine (DA), Epinephrine (E), and Norepinephrine (NE) before and after Naloxone in Normotensive Patients Receiving Halothane Anesthesia*

	Before naloxone	After 0.2 mg of naloxone	Before 0.4 mg of naloxone	After 0.4 mg of naloxone
MAP (torr)	88.66 ± 2.6	87.5 ± 2.5	87.5 ± 2.5	87.5 ± 2.5
HR (beats/min)	77 ± 1.7	77 ± 2	79 ± 2.3	79 ± 2.3
DA (pg/ml)	37.66 ± 9.7	22.22 ± 8.3	22.66 ± 5.9	27.5 ± 9.3
E (pg/ml)	37 ± 4.6	37.33 ± 4.6	45 ± 5.4	51.5 ± 7.3
NE (pg/ml)	306.5 ± 20.4	345.16 ± 38.6	310.83 ± 44.8	312.5 ± 44.6

* Values are means ± SE; n = 6.

TABLE 2

Mean Arterial Pressure, Heart Rate, and Plasma Levels of Dopamine, Epinephrine, and Norepinephrine before and after Naloxone in Hypertensive Patients Receiving Halothane Anesthesia*

	Before naloxone	After 0.2 mg of naloxone	Before 0.4 mg of naloxone	After 0.4 mg of naloxone
MAP (torr)	103.3 ± 5.6	104.6 ± 0.9	101.6 ± 1.5	102.8 ± 1.6
HR (beats/min)	75 ± 2	74 ± 2	74 ± 2	74 ± 2
DA (pg/ml)	29.3 ± 10.3	34.3 ± 13	41.2 ± 10	48.7 ± 14
E (pg/ml)	43 ± 13	68.3 ± 15.4	67.3 ± 9	63.2 ± 9
NE (pg/ml)	318.83 ± 34	334.6 ± 42	329.8 ± 25	385 ± 31

* Values are means ± SE = 6.

TABLE 3

Mean Arterial Pressure, Heart Rate, and Plasma Levels of Dopamine, Epinephrine, and Norepinephrine before and after Naloxone in Normotensive Volunteers without Anesthesia*

	Before naloxone	After 0.2 mg of naloxone	Before 0.4 mg of naloxone	After 0.4 mg of naloxone
MAP (torr)	88.66 ± 2.7	87.5 ± 2.5	87.5 ± 2.5	87.5 ± 2.5
HR (beats/min)	71 ± 1.8	70 ± 2	69 ± 2.3	69 ± 2.3
DA (pg/ml)	7.16 ± 4.7	20.5 ± 1.2	13.16 ± 4.4	11.3 ± 4.3
E (pg/ml)	32.5 ± 5.6	32 ± 7.6	27.16 ± 5	31.83 ± 6.8
NE (pg/ml)	262.3 ± 17.3	256 ± 23.5	245 ± 16.5	228.3 ± 22.3

* Values are means ± SE; n = 6.

TABLE 4

Mean Arterial Pressure, Heart Rate, and Plasma Levels of Dopamine, Epinephrine, and Norepinephrine before and after Naloxone in Hypertensive Volunteers without Anesthesia*

	Before naloxone	After 0.2 mg of naloxone	Before 0.4 mg of naloxone	After 0.4 mg of naloxone
MAP (torr)	100.6 ± 6	100.6 ± 6	101.6 ± 5.6	101.2 ± 5.7
HR (beats/min)	72.4 ± 1.9	69.4 ± 3.4	69.4 ± 3.4	70.2 ± 2.9
DA (pg/ml)	99 ± 60.7	88.4 ± 48.9	93.8 ± 47	125 ± 61.8
E (pg/ml)	43.8 ± 9.5	34.2 ± 6.3	53.8 ± 16	64.6 ± 29
NE (pg/ml)	195.8 ± 22	169 ± 23	204.4 ± 24	261.4 ± 42

* Values are means ± SE; n = 5.

Freye (13) believes that naloxone competes with narcotics for receptor sites in the central nervous system, displaces some of their molecules, and thus precipitates the "low dose effect" of narcotics, namely liberation of E from the adrenal medulla. Laverty and Roth (14) demonstrated that administration of naloxone to rats pretreated with morphine for 5 days was accompanied by an increased loss of NE from all brain regions when NE synthesis was inhibited by alpha-methyltyrosine. This finding is consistent with the electrophysiologic observations and suggests that morphine withdrawal induces an increase in the activity of brain noradrenergic neurones. This increase in the activity of brain noradrenergic neurons caused by narcotic reversal with naloxone stimulates the increased synthesis of NE. Naloxone administered to control rats (rats that did not receive morphine) had no significant effect on NE turnover.

Several factors affect circulating catecholamines in humans. Halter et al (15) observed that barbiturates and halothane suppress plasma levels of E, whereas surgical stimulation significantly increases plasma levels of NE and E above those present under anesthesia. Our surgical patients had higher mean catecholamine levels than our volunteers who were not receiving anesthesia or surgical stimulus but this difference was not statistically significant. The half-life of catecholamines in the circulation is less than 2 minutes, during which time they are rapidly inactivated by metabolism or re-uptake into sympathetic nerves (16, 17). We avoided the purported effects of surgery by collecting our samples when surgical stimulation was absent, or at a minimum, and at a time when anesthetic depth appropriate for the ongoing surgical procedure had been maintained for at least 1 hour. Our second blood samples were drawn 5 minutes after IV naloxone, as Patschke et al (12) noted that the increases in heart rate, systemic arterial pressure, coronary blood flow, cardiac output, and peak left ventricular pressure rate of increase reached a maximum during the first 5 minutes following IV naloxone and did not return to control values even

after 10 minutes. Tanaka (1) described an increase in blood pressure that began 3 minutes after IV naloxone which peaked at 10 minutes. Buhler et al (18) observed a significant increase in catecholamine levels during and up to 5 minutes after restraint stress in rats. Cryer et al (19) measured changes in plasma levels of catecholamine in humans associated with changes from the supine to the standing position 2, 5, and 10 minutes after the change in position. Plasma catecholamine levels began to increase at 2 minutes and significant increases occurred after 5 minutes. A similar finding was observed by Christensen (20), who also found that increases in catecholamine levels were related to an increase in heart rate among control subjects. Although catecholamines have a plasma half-life of less than 2 minutes, naloxone must circulate to its effector site before its action is exhibited. Our third blood samples were taken 30 minutes after injection of naloxone, based on the fact that plasma levels of IV naloxone, 0.4 mg, decline rapidly within 2 minutes and are almost absent within 20 minutes (21).

Hypertensive patients are thought to have higher plasma catecholamine levels than normotensive subjects (22–24). On the other hand, however, plasma NE levels increase with age (25) and age-adjusted plasma NE levels are similar in normotensive and hypertensive patients (26). Our normotensives were younger (mean age 35.9 years) than our hypertensives (mean age of 50.2 years) which may explain why catecholamine levels in our hypertensives tended to be higher. Plasma DA exists mostly in the conjugated form, only 17% being free, in contrast to plasma NE and E which are almost exclusively unconjugated (27) (99%). Our DA levels tended to be higher in the anesthetized patients except for one hypertensive volunteer whose DA levels was more than twice the normal range, which explains our high standard error for DA among the hypertensive volunteers. Factors affecting the conjugation of DA may help to explain these differences.

It was not possible to exclude patients receiving hypertensive medications that may alter plasma catecholamine levels. Many of our patients and two volunteers had been treated with alpha-methyldopa and hydrochlorothiazide. Hydrochlorothiazide has been reported to increase catecholamine levels (28), whereas alpha-methyldopa depletes NE and DA content of the medullary nuclei (29). None of our subjects received these medications less than 12 hours before blood sampling. The maximal effects of alpha-methyldopa on plasma levels of DA occurs after 4 hours and on NE at approximately 12 hours (29). This may explain the higher mean NE level in our normotensive volunteers when compared with the mean NE level in the hypertensive volunteers who had received alpha-methyldopa 12 hours before the study.

Diazepam, if given in a dose of 3 mg/kg, reduces the formation of dopa in the rat brain (30) which inhibits the first step in the synthesis of DA and NE. The half-life of diazepam is 20 to 90 hours (31). Our blood samples were taken approximately 3 to 4 hours after diazepam premedication of 0.1 mg/kg in our operative patients, a dose much lower than that mentioned above.

One patient in the anesthetized hypertensive group received pancuronium bromide, 0.04 mg/kg, more than 1 hour before blood sampling. Docherty et al (32) reported that pancuronium bromide blocks neuronal uptake of NE. The plasma half-life of pancuronium in humans is less than 5 minutes (33); increases in heart rate and blood pressure following intravenous pancuronium bromide at doses of 0.1 mg to 10 mg/kg reach a maximum within 0.5 to 5 minutes and decrease to base line levels within 2 to 10 minutes, the duration of the response being most prolonged with 10 mg/kg. With a dose of 0.04 mg/kg, as in our one subject, the effect should be even shorter than 10 minutes.

Based on our data and the previous work outlined we conclude that IV naloxone, 0.2 and 0.4 mg, without previously administered opiates causes neither hemodynamic changes nor increased levels of plasma catecholamines in normotensive or hypertensive humans whether anesthetized or awake. If sudden awakening and perception of pain result after IV naloxone, catecholamine levels may increase due to increased synthesis of NE triggered by the increase in the activity of brain-noradrenergic neurons and increased release of E from the adrenal medulla.

REFERENCES

1. Tanaka GY. Hypertensive reaction to naloxone. JAMA 1974;228:25–6.
2. Flacke JW, Flacke WE, Williams GD. Acute pulmonary edema following naloxone reversal of high-dose morphine anesthesia. Anesthesiology 1977;47:376–8.
3. Michaelis LL, Hickey PR, Clarke TA, Dixon WH. Ventricular irritability associated with the use of naloxone hydrochloride. Ann Thorac Surg 1974;18:608–14.
4. Azar I, Turndorf H. Severe hypertension and multiple atrial premature contractions following naloxone administration. Anesth Analg 1979;58:524–5.
5. Andree RA. Sudden death following naloxone administration. Anesth Analg 1980;59:782–4.
6. Desmonts JM, Bohm G, Couderc E. Hemodynamic responses to low doses of naloxone after narcotic-nitrous oxide anesthesia. Anesthesiology 1978;49:12–6.

7. Estilo AE, Cottrell JE. Naloxone, hypertension, ruptured cerebral aneurysm. Anesthesiology 1981;54:352.
8. Holaday JW, Faden AI. Naloxone reversal of endotoxin hypotension suggests role of endorphins in shock. Nature 1978;275: 450–1.
9. Faden AI, Jacobs TP, Holaday JW. Opiate antagonist improves neurologic recovery after spinal injury. Science 1981;211: 493–4.
10. Saller CF, Zigmond MJ. A radio enzymatic assay for catecholamines and dihydroxyphenylacetic acid. Life Sci 1978;23:1117–30.
11. De Prada M, Zurcher G. Simultaneous radio enzymatic determination of plasma and tissue adrenaline, noradrenaline and dopamine within the fontomole range. Life Sci 1978;9:1161–74.
12. Patschke D, Eberlein HI, Hess W, Tarnow J, Zimmermann G. Antagonism of morphine with naloxone in dogs. Br J Anaesth 1977;49:525–32.
13. Freye E. Cardiovascular effects of high dosages of fentanyl, meperidine, and naloxone in dogs. Anesth Analg 1974;53:40–7.
14. Laverty R, Roth RH. Clonidine reverses the increased norepinephrine turnover during morphine withdrawal in rats. Brain Res 1980;182:482–5.
15. Halter JB, Pflug AE, Porte D Jr. Mechanism of plasma catecholamine increases during surgical stress in man. J Clin Endocrinol Metab 1977;45:936–43.
16. Roizen MF, Weise V, Moss J, Kopin IJ. Plasma catecholamines: arterial-venous differences and the influences of body temperature. Life Sci 1975;16:1133–44.
17. Whitby LG, Axelrod J, Weil-Malherbe H. The fate of H^3-norepinephrine in animals. J Pharmacol Exp Ther 1961;132: 193–201.
18. Buhler HU, DaPrada M, Haefely W, Picotti GB. Plasma adrenaline, noradrenaline and dopamine in man and different animal species. J Physiol 1978;276:311–20.
19. Cryer PE, Santiago JV, Shah S. Measurement of norepinephrine and epinephrine in small volumes of human plasma by a single isotope derivative method: response to the upright posture. J Clin Endocrinol Metab 1974;39:1025–9.
20. Christensen NJ. Plasma catecholamine in long term diabetics with and without neuropathy and in hypophysectomized subjects. J Clin Invest 1972;51:779–87.
21. Berkowitz BA, Ngai SH, Hempstead J, Spector S. Disposition of naloxone: use of a new radioimmunoassay. J Pharmacol Exp Ther 1975;195:499–504.
22. De Quatro V, Chan S. Raised plasma catecholamine in some patients with hypertension. Lancet 1972;1:806–9.
23. Engelman K, Portnoy B, Sjoerdsma A. Plasma catecholamine concentrations in patients with hypertension. Circ Res 1970;27: 141–6.
24. Louis WJ, Doyle AE, Anavekar S. Plasma norepinephrine levels in essential hypertension. N Engl J Med 1973;288:599.
25. Pedersen EB, Christensen NJ. Catecholamines in plasma and urine in patients with essential hypertension. Acta Med Scand 1975;198:373–7.
26. Lake CR, Zeigler MG, Coleman MD, Kopin LJ. Age adjusted plasma norepinephrine levels are similar in normotensive and hypertensive subjects. N Engl J Med 1971;296:208–9.
27. Kuchel O, Bun NT, Unger TH, Genest J. Free and conjugated catecholamines in human hypertension. Clin Sci 1978;55:77S–80S.
28. Lake CR, Zeigler MG, Coleman MD, Kopin IJ. Hydrochlorothiazide-induced sympathetic hyperactivity in hypertensive patients. Clin Pharmacol Ther 1979;26:428–32.
29. Conway EL, Louis WJ, Jarrott B. The effect of alpha methyldopa administration on catecholamine levels in anterior hypothalamic, preoptic and medullary nuclei in rat brain. Neuropharmacology 1979;18:279–86.
30. Biswas B, Carlsson A. On the mode of action of diazepam on brain catecholamine metabolism. Naunyn Schmiedebergs Arch Pharmacol 1978;303:73–8.
31. Goodman LS, Gilman A. The pharmacological basis of therapeutics. 6th ed. New York: Macmillan Publishing Co, Inc, 1980: 350, 1702.
32. Docherty JR, McGrath JC. Sympathomimetic effects of pancuronium bromide on the cardiovascular system of the pithed rat. Br J Pharmacol 1978;64:589–99.
33. Agoston S, Kersten UW, Meijer DKF. The fate of pancuronium bromide in man. Acta Anaesthesiol Scand 1973;17:267–75.

ANESTH ANALG
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An Electroencephalographic Study of 4-Aminopyridine

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SIA, R. L., BOONSTRA, S., WESTRA, P., HAENEN, H.T.M., AND WESSELING, H.: An electroencephalographic study of 4-aminopyridine. Anesth Analg 1982;61:354-7.

The electroencephalographic (EEG) effects of 4-aminopyridine (4-AP) given intravenously in therapeutic doses were studied in four conscious human volunteers. 4-AP (0.2 mg/kg) caused an increase of the occipital alpha peak frequency of 0.4 to 1.0 Hz. In the dose range of 0.2 to 0.3 mg/kg there was neither evidence for epileptic activity in the EEG nor were any clinical side effects observed. This dose of 4-AP was also found to antagonize diazepam-induced sleep in four volunteers. In addition 4-AP (0.3 mg/kg) hastened the recovery by a factor of 4 in four patients having endoscopic procedures under diazepam-nitrous oxide anesthesia.

Key Words: ANTAGONISTS, Neuromuscular relaxants: 4-aminopyridine.

CLASSIC analeptic drugs, such as tetrahydroaminoacridine, picrotoxin, and nikethamide, have little clinical application in daily practice (1). The main reasons include their small margin of safety with respect to central nervous system (CNS) side effects, their short durations of action when used as respiratory stimulants, and the unpredictability of responses.

Paskov, Stoyanov, and Micov (2) introduced 4-aminopyridine (4-AP) into clinical practice as an antagonist to non-depolarizing muscle relaxants. The site of this antagonism appears to be presynaptic in origin and consists mainly of an enhanced release of acetylcholine and other neurotransmitters of the central and peripheral nervous system (3-7). In a preliminary study, Sia et al (8) showed that postoperative fentanyl-induced respiratory depression in patients is antagonized by 4-AP, and Agoston et al (9) have recently described antagonism by 4-AP of ketamine-diazepam anesthesia in human volunteers. The renewed interest in the pharmacologic properties and clinical use of 4-AP prompted us to examine the effect of this drug on the central nervous system in conscious volunteers in the presence or absence of diazepam-induced sedation. In addition, the recovery time after diazepam-nitrous oxide anesthesia in patients was assessed in the presence and absence of 4-AP.

Methods

Volunteers

Four male volunteers (mean age 33 ± 6 years) free of metabolic, neurologic, or other systemic disorders participated on three occasions, 1 week apart, in the different experiments. The investigation was performed under nonblind but placebo-controlled conditions. On the day of the experiment, stimulants such as coffee and tea were avoided. During the experiments, the volunteers rested on a bed in a silent, semidark, and comfortable room. They could be observed from outside by means of a window. Cardiorespiratory resuscitation equipment was present and each volunteer had a slowly running intravenous infusion of saline in his left arm.

Frontal and occipital EEG (F3 → C3, F4 → C4, and O1 → C3, O2 → C4; international 10/20 system) with closed eyes and ECG and respiratory impedance were recorded continuously using an Elema-Schönander polygraph. EEG analogue signals were recorded with

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a RC-time of 1.2 seconds and a high cut-off filter of 70 Hz. All data were recorded on paper and stored on tape (Honeywell 14-channel). An experienced electroencephalographist evaluated the recordings visually; the tapes were later computerized and compared with the visual evaluation. Frequency analysis was carried out on data epoch's of 5 seconds duration; after 30 seconds spectral parameters of EEG frequency bands were calculated.

On each occasion, one of the following schedules was executed: (*a*) A control period of 20 minutes, then a 30-minute observation period after a rapid intravenous bolus injection of 0.9% NaCl (placebo), then a 30-minute observation period after 4-AP (0.2 mg/kg as the free base; 5 mg/ml) was administered rapidly intravenously and, finally, a period of 30 minutes in which the effects of diazepam (0.1 mg/kg IV) were observed (n = 4). (*b*) Same schedule, but 4-AP was administered in a dose of either 0.2 or 0.3 mg/kg (each n = 2), diluted to 20 ml in 0.9% NaCl, over a period of 2 minutes and injected into a fast-running infusion. This mode of administration was chosen in order to avoid complaints of deep aching pain in the arm receiving the injection (10). (*c*) A control period of 20 minutes, then a 30-minute observation period after a rapid bolus injection of diazepam (0.1 mg/kg IV; n = 4).

Patients

A clinical study was performed in eight adult patients undergoing short endoscopic procedures of the larynx and esophagus. They received premedication consisting of diazepam, 10 mg, by mouth or by suppository and were anesthetized using only diazepam, 0.4 to 0.6 mg/kg, while breathing 67% nitrous oxide in oxygen. Recovery time was calculated as being the time from the end of surgery until the patient was able to open his eyes and respond verbally to commands. At the end of surgery, patients received either 4-AP, 0.3 mg/kg (n = 4), or saline (n = 4) intravenously.

Statistics

Arithmetic means with standard errors of the mean are presented. Statistical significance was tested using the paired Student's *t*-test with a 95% significance level.

Results

4-AP in a dose of 0.2 mg/kg IV caused the control occipital alpha peak frequency of 10.5 ± 0.2 Hz to increase by 0.4 to 1.0 Hz (mean 0.7 Hz; $p < 0.01$) in the conscious volunteers (Table 1). This increase was reached within 3 minutes and remained stable over the 4-AP observation period (Figure). Occipital beta-, delta-, and theta-activities were not significantly changed by 4-AP. 4-AP did not influence frontal EEG-activities.

Slow bolus injection of diluted 4-AP (0.2 or 0.3 mg/kg) over 2 minutes had the same effect on occipital alpha peak frequency, without evidence of dose dependency (Table 1). The EEG tracing of the volunteers showed no evidence of epileptic activity following this dose range of 4-AP administration.

After 4-AP observation period, diazepam, 0.1 mg/

TABLE 1

Results after Administration of 4-AP (0.2 or 0.3 mg/kg IV) and Diazepam (0.1 mg/kg IV) with (n = 4) or without (n = 4) Preceding 4-AP

Patient no.	Dose of 4-AP	Mode of administration of 4-AP (IV)	Mean control occipital alpha peak frequency	Mean increase in occipital alpha peak frequency after 4-AP	Level of consciousness after diazepam	
					With preceding 4-AP	Without preceding 4-AP
				Hz		
4-AP followed by diazepam with or without preceding 4-AP						
1	0.2	Quick bolus (10 sec)	10.7	0.5	Awake	Asleep
2	0.2	Quick bolus	10.2	0.8	Awake	Asleep
3	0.2	Quick bolus	10.0	0.4	Awake	Asleep
4	0.2	Quick bolus	11.0	1.0	Awake	Asleep
4-AP only						
1	0.3	Slow bolus (2 min)	10.7	0.5	—*	
2	0.3	Slow bolus	11.5	0	—	
3	0.2	Slow bolus	9.8	1.2	—	
4	0.2	Slow bolus	11.3	1.0	—	

* —, Absence of diazepam.

kg, was administered and on the subsequent diazepam observation period no sedative effect was noted. Furthermore, all four volunteers remained conscious during this period and this was confirmed by EEG findings (occipital alpha rhythm 8 to 13 Hz). This was in contrast to the sleep, characterized by the changed alpha-activity (stages 1 and 2 of sleep) that always occurred when diazepam was given without prior 4-AP treatment (Table 1).

One volunteer, who slept spontaneously during the control and placebo periods, awoke after administration of 4-AP and did not fall asleep when diazepam was injected. The increase in frontal beta-activity after diazepam was not influenced by 4-AP premedication. Heart rate showed a long and stable decrease (mean 16%) after 4-AP compared with control and placebo periods; this decrease was nearly abolished by diazepam (Figure and Table 2). Respiratory rate showed no significant change after 4-AP.

All volunteers later reported perioral paresthesias lasting 1 to 5 minutes after administration of 4-AP and complained of deep aching pain in the arm receiving the injection lasting at least 30 minutes. Even if 4-AP was diluted and injected slowly it proved impossible to abolish this adverse effect completely.

In patients undergoing endoscopic procedures 4-AP produced a statistically significant antagonism of diazepam-nitrous oxide anesthesia. Patients (n = 4) who received 4-AP had a mean recovery time of 6 ± 1 minutes, whereas the corresponding time for patients (n = 4) who did not receive 4-AP was 24 ± 3 minutes ($p < 0.005$). There were no side effects associated with 4-AP in these patients.

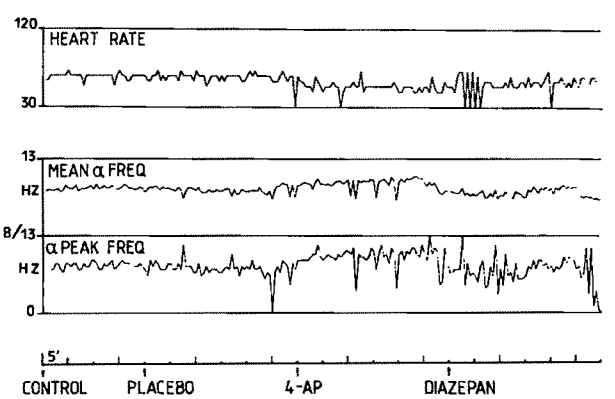


FIGURE. Digital output recording of heart rate, mean occipital alpha frequency, and alpha peak frequency during control, placebo, 4-AP (0.2 mg/kg IV), and diazepam (0.1 mg/kg IV) observation period. Heart rates of 30 beats per minute, which intermittently appear, are artifacts.

TABLE 2

Heart Rate and Respiratory Rate (n = 4) during Control Period and after Placebo, 4-AP (0.2 mg/kg IV), and Diazepam (0.1 mg/kg IV)*

	Control period	After administration of:		
		Placebo	4-AP	Diazepam
Heart rate	74 ± 5	74 ± 5	62 ± 4†	70 ± 5
Respiratory rate	13 ± 3	13 ± 2	13 ± 2	14 ± 1

* Values are means ± SEM.

† Statistically significantly different from control values.

Discussion

The pharmacologic properties of the aminopyridines (APs) have been investigated in vitro and in vivo since 1928. Dingemanse and Wibaut (11) observed strychnine-like convulsions in frogs receiving 2-AP and 3-AP. Shaw and Bentley (12) showed 2-AP and 4-AP to be respiratory stimulants in rabbits during morphine-induced respiratory depression. The same phenomenon was observed for 4-methyl-2-AP in morphine-treated rabbits (13). Direct stimulation of respiration by 2-AP, 3-AP, and 4-AP in cats was demonstrated by Fastier and McDowall (14). An increase of phrenic nerve activity, due to the central action of 4-AP, has also been reported in cats (15). Other pharmacologic properties of the APs observed in vitro or in animals include peripheral vasoconstriction, contraction of the smooth musculature of the intestine (14), sympathomimetic action on the vas deferens (3) and portal veins (16), positive inotropic effect on the heart, and significant increases in arterial blood pressure, left ventricular dp/dt max, and myocardial oxygen consumption (17, 18). These cardiovascular effects of 4-AP would appear to contraindicate its use in patients with arterial hypertension and coronary artery disease.

The dose of 4-AP used in this study (0.2 to 0.3 mg/kg) lies within the range used clinically to antagonize the effects of neuromuscular blocking agents (19) and fentanyl (8). The increase in occipital alpha frequency is indicative of an increase in the level of vigilance in the volunteers. One possible explanation is a direct effect of 4-AP on the CNS. Deep aching pain [observed by Lund, Nilsson, and Rosen (10)] could also indirectly increase vigilance in the volunteers. The latter is not likely, however, as there was no accompanying increase of heart rate. The effect of 4-AP on diazepam-induced sleep is more indicative of a direct stimulating effect of 4-AP on the CNS. This increased level of vigilance produced by 4-AP lasts at least ½ to 1 hour.

Although the sleep due to diazepam was antagonized by 4-AP, the prominent effect of diazepam on EEG, i.e., increased frontal beta-activity, was not affected. The EEG changes correlated with the increased level of consciousness in the presence of 4-AP. After diazepam there was a decrease in the occipital alpha rhythm slightly less than the level of the control values but still within the normal awake range (occipital alpha rhythm 8 to 13 Hz). However, none of the four volunteers slept after diazepam preceded by 4-AP in contrast to the same volunteers who slept after diazepam in the absence of 4-AP. It has been shown that after diazepam the occipital alpha rhythm decreases in amplitude and intensity to low voltage 4 to 6 Hz (stage 1 sleep) whereas in stage 2 sleep, there is an increase in theta and sigma activities (20). The effect of 4-AP on diazepam-induced changes in occipital alpha activity in volunteers was reflected by the arousal responses of the patients given 4-AP. The increased effect of diazepam on heart rate ($p < 0.05$) associated with 4-AP cannot be readily explained and probably represents the result of indirect effects of diazepam on the cardiovascular system (21, 22).

In conclusion, apart from its use as an antagonist to non-depolarizing relaxants, 4-AP also appears to have potentially useful analeptic properties, at least following diazepam, without inducing seizure activity.

ACKNOWLEDGMENTS

We wish to thank Y. Talsma for technical assistance and R. Carpay for preparing the manuscript.

REFERENCES

1. Franz DN. Central nervous system stimulants. In: Goodman LS, Gilman A, eds. The pharmacological basis of therapeutics. 6th ed. New York: Macmillan, 1980:585–91.
2. Paskov DS, Stoyanov NA, Micov VZ. New anticurare and analeptic drug pymadin (4-aminopyridine hydrochloride) and its use in anesthesia (in Russian). Eksp Khir Anesteziol 1973;18: 48–52.
3. Johns A, Golko DS, Lauzon PA, Paton DM. The potentiating effects of 4-aminopyridine on adrenergic transmission in the rabbit vas deferens. Eur J Pharmacol 1976;38:71–8.
4. Lundh H, Leander S, Thesleff S. Antagonism of the paralysis produced by botulinum toxin in the rat. J Neurol Sci 1977a;32: 29–43.
5. Lundh H, Thesleff S. The mode of action of 4-aminopyridine and guanidine on transmitter release from motor nerve terminals. Eur J Pharmacol 1977b;42:411–12.
6. Molgo J, Lemeignan M, Lechat P. Effects of 4-aminopyridine at the frog neuromuscular junction. J Pharmacol Exp Ther 1977;203:653–63.
7. Vizi ES, van Dijk J, Foldes FF. The effect of 4-aminopyridine on acetylcholine release. J Neural Transm 1977;41:265–74.
8. Sia RL, Salt PJ, Langrehr D, Agoston S, Erdmann W. Effects of the analeptic drug, 4-aminopyridine, upon post-operative respiratory depression in patients: a preliminary study. Acta Anaesthesiol Belg 1979;30:195–9.
9. Agoston S, Salt PJ, Erdmann W, Hilkemeijer T, Bencini A, Langrehr D. Antagonism of ketamine-diazepam anaesthesia by 4-aminopyridine in human volunteers. Br J Anaesth 1980;52: 367–70.
10. Lundh H, Nilsson O, Rosen I. Effects of 4-aminopyridine in myasthenia gravis. J Neurol Neurosurg Psychiatry 1979;42:171–5.
11. Dingemanse E, Wibaut JP. Zur Pharmakologie von einigen Pyridylpyrrolen und einigen Abkömmlingen des α-Aminopyridins. Naunyn Schmiedebergs Arch Pharmacol 1928;132:365–81.
12. Shaw FH, Bently G. Morphine antagonism. Nature 1952;169: 713–4.
13. Von Haxthausen E. Über Amino-pyridin und seine Derivate. Arch Exp Pathol Pharmakol 1955;226:163–71.
14. Fastier FN, McDowall MA. A comparison of the pharmacological properties of the three isomeric aminopyridines. Aust J Exp Biol Med Sci 1958;36:365–72.
15. Folgering H, Rutten J, Agoston S. Stimulation of phrenic nerve activity by an acetylcholine releasing drug: 4-aminopyridine. Pfluegers Arch 1979;379:181–5.
16. Leander S, Anders A, Johansson B. Effects of 4-aminopyridine on mechanical activity and noradrenaline release in the rat portal vein in vitro. Eur J Pharmacol 1977;46:351–61.
17. Bowman WC, Marshall RJ, Rodger IW, Savage AO. Actions of 4-aminopyridine on the cardiovascular systems of anaesthetized cats and dogs. Br J Anaesth 1981;53:555–65.
18. Martinez-Aguirre E, Wikinski JA, Bello A, Izquierdo J, Garcia A, Velarde H. Effect of 4-aminopyridine on cardiovascular functions in the dog. Can Anaesth Soc J 1981;28:114–20.
19. Stoyanov E, Vulchev P, Shturbova M, Marinova M. Clinical electromyomechanographic and electromyographic studies in decurarization with pymadine. Anaesth Resc Intens Ther 1976;4:139–42.
20. Rechschaffen A, Kales A. A manual of standardized serminology, techniques and scoring system for sleep stages of human subjects. Washington, DC: Government Printing Office, 1968.
21. Hockman CH, Livingston KE. Inhibition of reflex vagal bradycardia by diazepam. Neuropharmacology 1971;10:307–14.
22. Przybyla AC, Wang SC. Locus of central depressant action of diazepam. J Pharmacol Exp Ther 1968;163:439–47.

ANESTH ANALG
1982;61:358-61

Effect of Intranasal Cocaine on Experimental Pain in Man

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YANG, J. C., CLARK, W. C., DOOLEY, J. C., AND MIGNOGNA, F. V.: Effect of intranasal cocaine on experimental pain in man. Anesth Analg 1982;61:358-61.

Sixteen healthy male volunteers had 30 mg of cocaine HCl solution or normal saline placebo impregnated in cotton-covered applicators administered intranasally on different days in a double-blind procedure. Ischemic tourniquet pain was significantly less after cocaine than it was in pretreatment control. It was also significantly less than after administration of a placebo. Responses to questionnaires concerning subjective drug effects, mood, and alertness revealed little change in psychological status associated with either cocaine or placebo. Thus, the reported decrease in pain was probably not caused by a change in affect or by altered consciousness. These results indicate that, in addition to its known properties as a local anesthetic, cocaine when applied intranasally exerts an analgesic effect.

Key Words: ANESTHETICS, Local: cocaine; PAIN: experimental, ischemic.

CLINICALLY, cocaine is used as a local anesthetic, whereas socially its use has been abused because it produces euphoria. Sluder (1) first reported the use of intranasal cocaine to relieve the symptoms and signs of the "syndrome of nasal (sphenopalatine-Mickel's) ganglion neurosis." Patients with the syndrome suffered from pain at the root of the nose, radiating to the occiput. In severe attacks, pain could spread to neck, shoulder, and hands. Because the syndrome is of wide distribution and frequently associated with vasomotor and secretory phenomena, such as nasal congestion with abundant secretion and dilation of pupils, S. Ruskin (2) postulated it might be related to the irritation of the nasal sympathetic system. He further suggested that this could lead to diffuse effect in the autonomic nervous system and interfere with microcirculation of the voluntary muscles of the trunk and extremities. Stewart and Lambert (3) also reported successful treatment of headache, and neck and shoulder pain with intranasal application of cocaine on the sphenopalatine ganglion. Currently, many clinicians use this technique to treat pain in various parts of the body, as reviewed by A. Ruskin (4). However, the possibility that cocaine may exert systemic analgesic effect when applied in this manner remains controversial. It is partly due to the last of strict scientific discipline in the available literature which leds to the criticism that the pain relief could be due to euphoria or other psychological changes.

The site of application, intranasal, is of importance. Twycross (5) reported that oral cocaine in a Brompton cocktail had little effect on relief of cancer pain. Although cocaine has been investigated extensively (6), its analgesic action has not been studied with intravenous injection. The purpose of this study was to determine whether intranasal application of cocaine exerts an analgesic effect on experimentally induced pain. A double-blind procedure was used. The dose of cocaine was kept small to avoid possible influence of its euphoric effect on pain report. The volunteer's psychological status was monitored by questionnaires throughout the experiment.

Methods and Materials

The protocol was approved by the Institutional Review Board for Human Investigation of Columbia

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Supported in part by National Institutes of Health Grant GM-26461-01.
Received from the Departments of Anesthesiology, Psychiatry, and Otolaryngology, College of Physicians & Surgeons, Columbia University, New York, New York. Accepted for publication December 24, 1981. Presented in part at the Annual Meeting of the American Pain Society, September 6, 1980, New York, New York.

University. Sixteen healthy young male volunteers without previous exposure to cocaine were told that they would receive cocaine and saline on different days. Possible physical and psychological effects of the experiment were described, and the volunteers signed an informed consent form. The tests were performed at about the same time of the day on two occasions, approximately 1 week apart. Both the subject and the experimenter were "blind" with respect to which of the two substances was administered. Drug treatments (that is, administration of cocaine or placebo intranasally) were randomized over days. The arms used for ischemic tourniquet pain were also alternated with respect to dominance.

Each session began with a pretreatment control period during which ischemic pain was induced. In a sitting position, the volunteer extended his arm upward while an Esmarch bandage was wrapped around the hand and arm to exsanguinate the extremity. An automatic tourniquet was placed around the arm and inflated to 250 torr. The bandage was removed, and the subject squeezed a hand dynamometer to half of his maximum strength for two 10-second periods. The subject then started to report his sensory experience every 10 seconds for 15 minutes by pointing at a scale consisting of six categories: nothing, slight sensation, strong sensation, slightly painful, definitely painful, severely painful. Under each category a column of numbers from 1 to 26 appeared, the higher numbers meaning stronger sensation; this numerical score was used by the subject to report small changes in sensory experience occurring within a verbal score category.

The drug treatments (cocaine or placebo) began approximately 15 minutes after the sensation of the arm had completely recovered following the pretreatment control ischemic period. The nasal mucosa was sprayed with 1% cocaine solution through a De Vilbiss atomizer by squeezing the bulb three times. The amount of 1% cocaine used in the spray was approximately 0.1 ml. It was used for two purposes. First, it made the insertion of the applicator less uncomfortable. Second, it served as an active placebo to keep the volunteers blind because the spray would cause some degree of nasal vasoconstriction and give a bitter taste. Then two cotton-covered nasal applicators, impregnated either with 0.15 ml of 10% cocaine or 0.15 ml of 0.9% saline, were inserted behind the middle turbinate through the nostrils on both sides. To ensure blindness shortly after insertion of the applicator, volunteers were asked whether there was any special feeling in the mouth and throat. Only one reported tasting bitterness, and he was excluded from the study. Fifteen minutes later, the applicators were removed and the tourniquet procedure was repeated on the other arm.

Two volunteers failed to complete 15 minutes of the ischemic pain test. The tourniquet had to be deflated at 12 and 14 minutes, respectively, in the control period. Their last sensory reports before the test was stopped were assumed to be the report they would give had the experiment gone on for 15 minutes.

For analysis of the data, the verbal report category "nothing" was assigned a rating of 1, while each of the remaining five verbal report categories, "slight sensation" to "severe pain," was divided into three variables: low, average, and high; these values were obtained to divide the range of the numerical score of each subject within each verbal category by three. The subject's sensory response was based on the median value obtained from the six responses (10 seconds each) made during each minute. Thus, the sensory rating ran from nothing, 1, through three levels of slight sensation, 2, 3, 4, etc, up to three levels of severely painful, 14, 15, 16. Details of the methodology used have been reported previously (7).

Analysis of variance was used to test the subjects' response medians for differences among treatments at each minute. When the F values obtained indicated that the mean of one treatment group was different from that of another, critical differences (CD) based on two-tailed *t*-tests (8), with each subject serving as his own control, were computed. The CD at each minute is the difference between means that must be met or exceeded in order to achieve significance.

To assess the subjective and psychological effects of the experiment, three questionnaires were used: the Spielberger State Anxiety Inventory (9), the Clark Drug Reaction Checklist (10), and an alertness scale. (The alertness questionnaire contains 10 questions: 1. My thoughts are fastmoving. 2. My thoughts are dreamlike. 3. My thoughts are incoherent. 4. My thinking is sluggish. 5. I feel low, unhappy. 6. I feel wide awake, alert. 7. I do not feel hungry. 8. I feel high, euphoric, 9. I cannot concentrate on anything. 10. I feel drowsy.) For each questionnaire, the four response categories: not at all, somewhat, moderately, and very much so, were given ordinal weights of 1, 2, 3, 4, respectively. Each questionnaire was administered before the tourniquet was applied in the pretreatment control period and 15 and 45 minutes after the nasal applicators were inserted. These data were treated by a sign test (11).

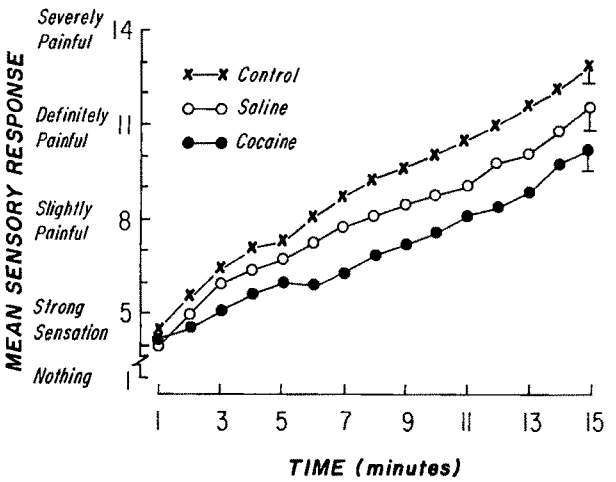


FIGURE. Effect of cocaine and saline on ischemic pain report in 16 subjects. Average standard errors for each treatment group are indicated with vertical bars at minute 15. There was significant analgesic effect in cocaine period relative to both saline and pretreatment control periods. There was also a smaller but significant placebo effect of saline period relative to control period. See text for level of significance related to time.

Results

Results of the mean sensory responses averaged over subjects appear in the Figure. As there was little difference between the control values on separate days, the data were averaged as one treatment. Analysis of variance revealed that the overall main effect of treatments (control, saline, and cocaine) was significant, $F(2, 30) = 8.17$, $p < 0.001$. The interaction of treatments and time was significant, $F(28, 420) = 3.00$, $p < 0.001$. The simple effect of treatments within each minute was significant from minutes 3 through 15, $F(2, 30) \geq 3.90$, $p < 0.05$. The critical difference, with each subject serving as his own control, was CD ≥ 1.18, $t(30) \geq 2.04$, $p \leq 0.05$. Thus the mean sensory responses during the cocaine treatment period were significantly less than those for the saline treatment period at minutes 6, 7, 8, 9, 12, 13, and 15. Relative to the pretreatment control period, the mean sensory response during the cocaine treatment period was significantly less at minutes 4 through 15. The mean sensory response during the saline placebo treatment period was significantly less than that during the control period at minutes 10 through 15, indicating a placebo effect.

Results of the data from the questionnaire appear in the Table. Positive changes are defined as follows: for the Spielberger State Anxiety Inventory, increased sense of well-being; for the Clark Drug Reaction Checklist, a larger magnitude of subjective drug effect; for the alertness scale, improved orientation. One

TABLE

Questionnaire Results*

Questionnaire	Pretreatment vs 15 min post-treatment	Pretreatment vs 45 min post-treatment
Spielberger		
Cocaine	62.50	62.50
Saline	68.75	62.50
Clark Drug Reaction Checklist		
Cocaine	87.50†	62.50
Saline	31.25	53.33‡
Mood-alertness		
Cocaine	37.50	37.50
Saline	37.50	31.25

* Comparison of subjective effects of treatments to pretreatment control period by percentage of subjects (n = 16) showing positive changes relative to pretreatment period. For each subject, subjective changes were classified as positive or negative by comparing posttreatment scores to pretreatment scores. In the event that treatments were without psychological effect, statistically 50% of subjects should have shown positive changes and 50% should have shown negative changes.

† $p < 0.05$, meaning 87.5% is significantly different from 50%.

‡ Based on n = 15 because of missing data.

significant difference between the periods was observed. By the method of sign test, which assumes neutral response would be 50% at 15 minutes after cocaine application, 87% of the subjects showed an increased response on the Clark Drug Reaction Checklist compared with the preexperimental period.

Discussion

In the search for treatment of patients who suffer from chronic pain, intranasal cocaine as described in this article has been found useful by many clinicians. Unfortunately, no double-blind controlled study has ever been reported for its efficacy. Furthermore, because of the complexity of pain report, factors such as placebo effect and euphoria induced by cocaine offer alternative explanations for reduced pain report. Our data show that in a double-blind study with little change in psychological status, cocaine applied intranasally has an analgesic effect on experimental ischemic pain.

The design of the study was to determine whether cocaine exerted a systemic analgesic effect with minimum involvement of euphoria, hence a small dose was used. Otherwise, induced euphoria could defeat the purpose of the double-blind procedure. This might be the reason that the analgesic effect demonstrated was significant but not striking. It is unlikely euphoria made any important contribution to the

analgesic effect because the psychological changes were minimal, there being only one statistically significant value out of 12 comparisons in the questionnaire data analyses.

The physiologic mechanism of this analgesic effect of cocaine is unknown. Two possibilities exist, namely, local or central effect. A. Ruskin (4) proposed that with the technique used, cocaine may block the sphenopalatine ganglion by locally anesthetizing the sympathetic ganglion; thus pain relief in a remote area might be achieved. Technically, it is possible to localize this site of action by using other local anesthetics such as tetracaine which is devoid of euphoric effect. But little would be gained by performing such an additional control study, for no method is available to verify objectively whether the sphenopalatine ganglion is specifically blocked.

On the other hand, it is possible that cocaine could exert this analgesic effect by its central action, either following absorption into the bloodstream or following diffusion to the brain due to the proximity of the location of drug application. Plasma cocaine levels after intranasal cocaine is applied in different dosages given as 10% aqueous solution (ranging from 0.19 to 2.0 mg/kg; the dose of 0.38 mg/kg was close to that used in our study) were determined by Wilkinson et al (12). They reported that plasma levels after intranasal cocaine peaked at a mean time of 57.6 ± 5.8 minutes for all doses. Yet Van Dyke et al (13), using 10% cocaine HCl, 2.0 mg/kg intranasally, observed in volunteers who rated themselves on a six-point "high" scale, the maximum subjective effect on the high score peaked from 15 to 60 minutes after drug administration. The discrepancy between serum level and psychological change suggests that a certain amount of intranasal cocaine activity may be due to the action of material passed through locally.

Forrest et al (14) reported that dextroamphetamine given intramuscularly augmented pain relief by morphine in postoperative patients. As cocaine also possesses a sympathomimetic effect, it would be tempting to hypothesize that cocaine analgesia might be related to endogenous catecholamines. On the other hand, it could be speculated that the possible specific central binding site for (^{3}H)-cocaine reported by Reith et al (15) in mouse brain membrane could play a role in its analgesic effect. But these data do not provide any conclusive evidence that could lead to any satisfactory explanation of the mechanisms of our results. Further investigations would be necessary to resolve this complex issue.

REFERENCES

1. Sluder G. The anatomical and clinical relations of the sphenopalatine ganglion of the nose. NY Med J 1909;90:293–8.
2. Ruskin SL. Neurologic aspects of nasal sinus infections: headaches and systemic disturbances of nasal ganglion origin. Arch Otolaryngol 1929;10:337–83.
3. Stewart D, Lambert V. Further observations on sphenopalatine ganglion. J Laryngol Otol 1934;49:319–23.
4. Ruskin AP. Sphenopalatine ganglion: remote effects including "psychosomatic" symptoms. Rage reaction, pain, and spasm. Arch Phys Med Rehabil 1979;60:353–9.
5. Twycross RG. Effect of cocaine in Brompton cocktail. Adv Pain Res Ther 1979;3:927–32.
6. Petersen RC, Stillman RC, eds: Cocaine: 1977. Research Monograph 13, National Institute on Drug Abuse, Washington, DC, 1977:35–38.
7. Yang JC, Clark WC, Ngai SH. Antagonism of nitrous oxide analgesia by naloxone in man. Anesthesiology 1980;50:414–7.
8. Winer BJ. Statistical principles in experimental design. New York: McGraw-Hill, 1962:89–92.
9. Spielberger CD, Gorsuch RL, Lushene RE. Manual for the State-Trait Anxiety Inventory. Palo Alto, CA: Consulting Psychologist Press, 1970.
10. Clark WC. Sensory-decision theory analysis of the placebo effect on the criterion for pain and thermal sensitivity. J Abnorm Psychol 1969;74:363–71.
11. Siegel S. Nonparametric statistics for the behavioral sciences. New York: McGraw-Hill, 1956:68.
12. Wilkinson P, Van Dyke C, Jatlow P, Barash P, Byck R. Intranasal and oral cocaine kinetics. Clin Pharmacol Ther 1980;27:386–94.
13. Van Dyke C, Jatlow P, Ungerer J, Barash PG, Byck R. Oral cocaine: plasma concentrations and central effects. Science 1978;200:211–3.
14. Forrest WH, Brown BW, Brown CR, et al. Dextroamphetamine with morphine for the treatment of postoperative pain. N Engl J Med 1977;296:712–5.
15. Reith MEA, Sershen H, Lajtha A. Saturable (^{3}H)-cocaine binding in central nervous system of mouse. Life Sci 1980;27:1055–62.

ANESTH ANALG
1982;61:362-5

Continuous and Simultaneous On-Line Measurements of $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ during Endotracheal Anesthesia

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RAMANATHAN, S., CHALON, J., SATYANARAYANA, T., ARISMENDY, J., AND TURNDORF, H.: Continuous and simultaneous on-line measurements of $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ during endotracheal anesthesia. Anesth Analg 1982;61:362-5.

A simple method was developed for the continuous measurement of oxygen consumption ($\dot{V}_{O_2}$) and carbon dioxide production ($\dot{V}_{CO_2}$) during endotracheal anesthesia. The total vented flow from a Bain circuit was measured during anesthesia in 28 adult patients and was found to attain at least 97% of a 6-L/min fresh gas inflow (FGI). Therefore, the circuit overflow was assumed to approximate the FGI. Total volume of vented oxygen was calculated by multiplying FGI by oxygen concentration in the vented (mixed expired) gas. $\dot{V}_{O_2}$ was assessed as the difference between the oxygen volumes entering and leaving the circuit. $\dot{V}_{CO_2}$ was derived from the product of FGI and mixed expired CO_2 concentration. $\dot{V}_{O_2}$ measured on the Bain circuit correlated with measurements made on a non-breathing circuit ($n = 60$ pairs, $r = 0.99$). A good correlation was also found between $\dot{V}_{CO_2}$ values obtained on both circuits ($n = 60$ pairs, $r = 0.99$).

Key Words: OXYGEN: consumption; CARBON DIOXIDE: production; ANESTHETIC TECHNIQUES: Bain circuit.

ASSESSMENT of oxygen consumption ($\dot{V}_{CO2}$) and carbon dioxide production ($\dot{V}_{CO2}$) is difficult during anesthesia using a circle absorber system because it necessitates measurement of total circuit flow and mean inspired and expired gas concentration (1). Total circuit flow is usually measured on special circuits either by collecting gas in a Douglas bag or by pneumotachography (2). Mean rather than instantaneous gas concentration must be known because the composition of the gas mixture varies during the respiratory cycle. Mean concentration is measured with an on-line microprocessor which integrates signals received from rapid gas analyzers (2). This report describes a simple method of $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ assessment during anesthesia when using a Bain circuit and requires only commonly available equipment.

Methods

The study was conducted on 57 patients divided into three groups of 28, 15, and 14 subjects. The protocol was approved by the Committee on Human Experimentation of the New York University Medical Center. All patients gave informed consent for the procedure.

In 28 patients (group A), aged 18 to 59 years and weighing 79 ± 8 kg (mean ± 1 SD), anesthesia was induced with thiopental (4 mg/kg) after 10 minutes of preoxygenation. Tracheal intubation was performed under succinylcholine-induced apnea. Anesthesia was maintained on a Bain circuit. A fresh gas inflow (FGI) of 6 L/min (N_2O = 4 L and O_2 = 2 L) with halothane 0.5% to 1% was used. All flowmeters had been calibrated on a Collins spirometer. Respiration was controlled using an Ohio anesthesia ventilator (fluidic model) in which circuit overflow and driving oxygen are vented separately. Minute volume was 120 ml/kg. Muscle relaxation was maintained with intermittent doses of pancuronium bromide. After 1 hour, the volume of gas vented from the respirator per minute was measured with a Collins spirometer. In addition, the humidity of gases at the respirator end of the circuit was measured in 10 patients with an on-line hygrosensor connected to an electric hygrometer indicator (Hydrodynamics Inc., Silver Springs, MD). Gas temperature at that site was assessed by telethermometry.

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Reprint requests to Dr. Ramanathan.

In 15 patients (group B), aged 15 to 45 years and weighing 72 ± 8 kg (mean ± 1 SD), anesthesia was conducted as in group A using a Bain circuit. Arterial blood pH and gas tensions were measured 1 hour after induction. Patients were then switched to a non-rebreathing circuit incorporating a Frumin valve. An Airshields Ventimeter ventilator was used to control respiration in this group because FGI inflates the ventilating bellows (unlike that of the Ohio model which is partly filled by gravity). This enabled suitable adjustment of the FGI to just fill the system. The respiratory minute volume needed to produce a Pa_{CO_2} approximately equal to that obtained on the Bain circuit (within 2 torr) was measured.

The last 14 patients (group C), aged 19 to 65 years and weighing 74 ± 8 kg (mean ± 1 SD), underwent prolonged superficial plastic surgery. Anesthesia was conducted using a Bain circuit as in group A. Respiration was controlled by an Ohio anesthesia ventilator at a tidal volume of 10 ml/kg and a rate of 12 breaths per minute. Mixed expired oxygen and CO_2 concentrations ($F\bar{E}_{O_2}$ and $F\bar{E}_{CO_2}$) were measured as shown in Fig 1. The capnograph pump aspirated circuit gases at a rate of 0.5 L/min from a T-piece attached to the respirator hose. Gases passed through a 1-L mixing bag, a water-separating tampon, and the infrared cell of a capnograph. Gases then entered the sensor manifold of a polarographic oxygen analyzer (model 402, Instrumentation Laboratory, Inc, Lexington, MA) and were returned to the circuit through a one-way valve which prevented back flow. The electrical output of the oxygen analyzer was recorded on a chart recorder (Linear Instruments, Irvine, CA). The recorder was used to determine fractional values because minimum resolution of the analyzer was 2%. The analyzer-recorder assembly was calibrated so that a 10% change in the analyzer meter reading produced a recorder deflection of 20 cm, thus improving resolution to 0.1%. The capnograph was calibrated with gas mixtures of known CO_2 concentrations. Corrections were applied for zeroing errors and the collision-broadening effects of N_2O (3). After 1 hour of anesthesia, $F\bar{E}_{O_2}$ and $F\bar{E}_{CO_2}$ were read. Total volume of oxygen vented from the circuit was calculated by multiplying FGI by $F\bar{E}_{O_2}$. $\dot{V}_{O_2}$ was assessed as the difference between volumes of oxygen in fresh gas (2 L) and in vented gas. Carbon dioxide production was taken as the product of the FGI and the $F\bar{E}_{CO_2}$. Patients were then switched to the non-breathing circuit described in group B. Minute ventilation was adjusted to produce a Pa_{CO_2} within 2 torr of values noted on the Bain circuit (based on the findings in group B). After 30 minutes all exhaled gases were collected in a Douglas bag for 5 minutes to measure volume and concentration of oxygen and carbon dioxide. Oxygen consumption was calculated as the exhaled minute volume times the difference between $F\bar{I}_{O_2}$ (oxygen concentration in fresh gas) and $F\bar{E}_{O_2}$. Carbon dioxide production was calculated as the exhaled minute volume times the $F\bar{E}_{CO_2}$. Sixty pairs of measurements of $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ were obtained on both the Bain and the non-rebreathing circuits and subjected to correlative analysis.

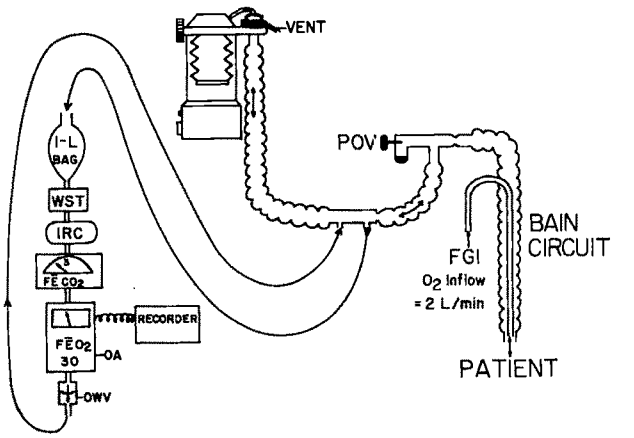


FIG 1. System used to measure $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$. POV, Pop-off valve; WST, water separating tampon; IRC, infrared cell; OA, oxygen analyzer; OWV, one-way valve; FGI, fresh gas inflow. Mixed expired CO_2 ($F\bar{E}_{CO_2}$) and ($F\bar{E}_{O_2}$) are 3% and 30%, respectively. Therefore, $\dot{V}_{CO_2}$ = 180 ml (6000 × 0.03) and $\dot{V}_{O_2}$ = oxygen in fresh gas-vented oxygen = 2000 − (6000 × 0.3) = 200 ml.

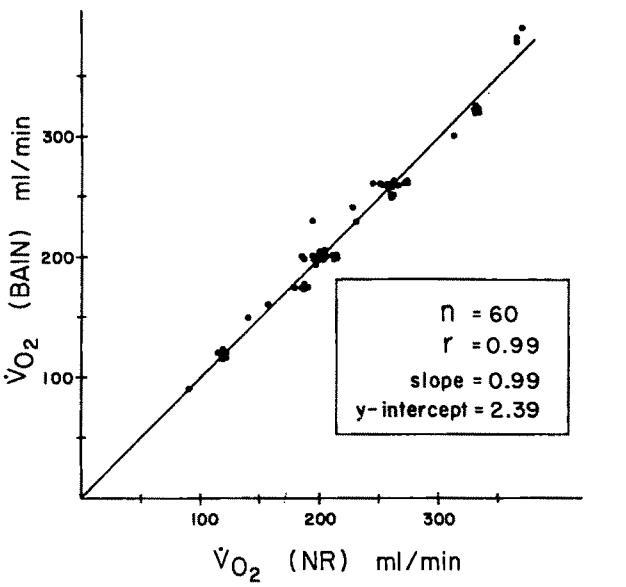


FIG 2. Correlative plot between $\dot{V}_{O_2}$ measured with non-breathing (NR) circuit and that measured with Bain circuit. $\dot{V}_{O_2}$ (NR), oxygen consumption measured with non-rebreathing circuit.

Results

In group A the mean total vented flow from the circuit (±1 SD) was 190 ± 53 ml lower than the FGI. The gases at the respirator end of the circuit were fully saturated with water vapor at 27.2 ± 1°C. In group B, a non-rebreathing respiratory minute volume of 110 ml/kg maintained Pa_{CO_2} within 2 torr of the Bain P_{CO_2}. In group C, $\dot{V}_{O_2}$ measured on the Bain circuit ($\dot{V}_{O_2}$ B) closely correlated with values obtained by the non-rebreathing (NR) technique ($\dot{V}_{O_2}$ NR, Fig 2, n = 60, range 90 to 380 ml, $r = 0.99$: $\dot{V}_{O_2}$ B = 0.99 × $\dot{V}_{O_2}$ NR + 2.39). $\dot{V}_{CO_2}$ B was closely related to $\dot{V}_{CO_2}$ NR (Fig 3, range 88 to 303 ml, $r = 0.99$: $\dot{V}_{CO_2}$ B = 1.04 × $\dot{V}_{CO_2}$ NR − 0.5). The mean $\dot{V}_{O_2}$ B was 222 ± 67 ml and the mean $\dot{V}_{O_2}$ NR 233 ± 68 ml. Corresponding $\dot{V}_{CO_2}$ values were 186 ± 61 ml and 179 ± 58 ml. Arterial pH and gas tensions are listed in the Table.

Discussion

The Bain circuit is a coaxial variant of the Mapleson D system. Conway (4) has shown that during the use of semiclosed rebreathing systems: (*a*) $\dot{V}_{O_2}$ = (FGI × F_{FO_2}) − ($\dot{V}v$ × Fv_{O_2}), where $\dot{V}v$ is the total vented gas flow from the circuit and Fv_{O_2} is the oxygen concentration in that gas or simply the difference between the quantities of oxygen entering and leaving the circuit, and (*b*) $\dot{V}_{CO_2} = \dot{V}v \times F\bar{E}_{CO_2}$. The gas mixture at the patient end of the Bain circuit is an inhomogeneous blend of fresh and exhaled gases. This is evidenced by the large fluctuations of CO_2 concentration noted during ventilation (Fig 4, A). However, the admixture between these two gases is more homogeneous at the respirator end of the circuit, in the respirator bellow, and its hose. This is shown by the marked reduction in CO_2 concentration fluctuation seen at these sites (Fig 4, B). As only a portion of the mixed expired gas is vented, any of these sites offers a convenient point for the monitoring of vented (mixed expired) gas concentration (5, 6).

In the absence of leaks, gas loss from the Bain circuit is due to anesthetic uptake by the patient and disparity between $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$. A hypothetical patient weighing 100 kg takes up approximately 300 ml of oxygen, 200 ml of N_2O, and 15 ml of halothane vapor from the circuit per minute after 1 hour of anesthesia (reference 7 and Loew HJ: Dosage schedules for closed system anesthesia, thesis, University

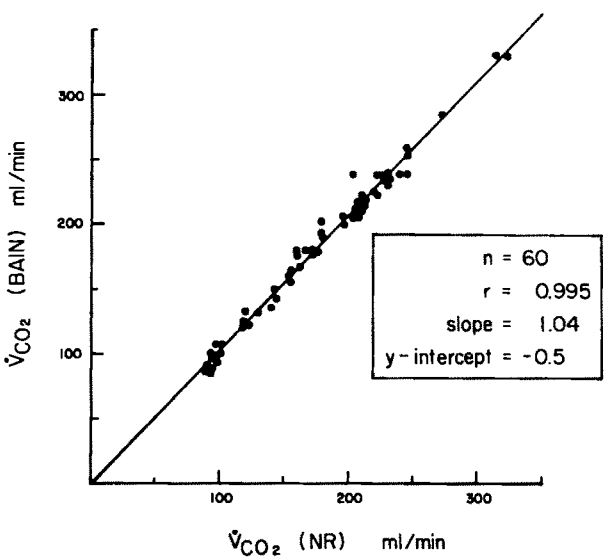


FIG 3. Correlative plot between $\dot{V}_{CO_2}$ measured with non-breathing circuit and that measured with Bain circuit. $\dot{V}_{CO_2}$ NR, Carbon dioxide production measured with non-rebreathing circuit.

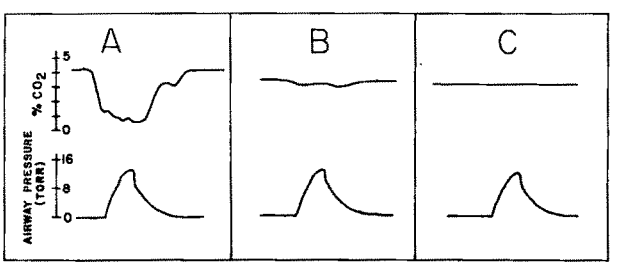


FIG 4. Carbon dioxide concentrations in Bain circuit during respiratory cycle. A, CO_2 concentration at patient end. B, CO_2 concentration at respirator end; gases were directly delivered to infrared cell. C, CO_2 concentration at respirator end of circuit; gases passed through a 1-L mixing bag before analysis. Note that in A, CO_2 concentration fluctuates widely with respiration, but in B, fluctuations are markedly diminished. In C, fluctuations are eliminated because of mixing bag in measuring system.

TABLE

Arterial pH and Gas Tensions of Patients Studied*

Parameter	Group A		Group B		Group C
	Bain	Non-rebreathing	Bain	Non-rebreathing	Bain
pH	7.38–7.45	7.37–7.48	7.38–7.48	7.4–7.48	7.36–7.46
Pa_{CO_2} (torr)	35.2 ± 4	34.2 ± 3	36 ± 4	34.5 ± 3	35 ± 3
Pa_{O_2} (torr)	150 ± 6	159 ± 8	155 ± 24	159 ± 8	162 ± 18

* Bain and non-rebreathing refer to types of anesthesia circuits used. Pa_{CO_2} and Pa_{O_2} are means ± 1 SD.

of Southern California, 1978). During the same period 240 ml of CO_2 is exhaled into the circuit. Therefore, the total loss of gas from the circuit could reach a theoretical maximum of 275 ml (330 ml of O_2, 200 ml of N_2O, and 15 ml of halothane less 240 ml of exhaled CO_2). However, in actual practice, gases in the circuit are loaded with water vapor (8). We measured the moisture at the respirator end of the circuit and found a water vapor content of 3.6% or 216 ml in a 6-L/min FGI. Thus, 79% of the gas lost by anesthetic uptake is replaced both by carbon dioxide and water vapor. Consequently, the total vented flow can be assumed to be equal to the FGI. One can say that $\dot{V}_{O_2}$ = total oxygen inflow less FGI × $F\bar{E}_{O_2}$), and $\dot{V}_{CO_2}$ = FGI × $F\bar{E}_{CO_2}$. The predicted $F\bar{E}_{O_2}$ and $F\bar{E}_{CO_2}$ in the hypothetical example are 0.285 (1700 ÷ 5966) and 0.04 (240 ÷ 5966). Therefore, $\dot{V}_{O_2}$ is equal to 290 ml [2000 − (0.285 × 6000)] (which is close to the actual $\dot{V}_{O_2}$ of the patient) and the $\dot{V}_{CO_2}$ = 0.04 × 6000 or 240 ml.

The mean measured difference between FGI and vented flow was 190 ml. However, the calculated difference in the hypothetical example was only 34 ml (6000 − 5966). This may be due to several factors including: (*a*) the outer tube of the Bain circuit is a common channel for both inspiration and expiration, thus there is significant water condensation in the cooler respirator end of the circuit, in the respirator bellows, and in the spirometer (which was at 20 ± 1.2°C); (*b*) the patient exhales water vapor saturated at 32°C during endotracheal anesthesia (8), a total of 143 ml of water vapor (the difference between saturated humidities at 32 and 20°C) could have condensed in the respirator bellow, spirometer, and the hose which connected the spirometer to the respirator vent; and (*c*) variations in atmospheric pressure and imperceptible leaks in the system. Although a water-separating tampon was used at the capnograph inlet, it was found (by electric hygrometry) effective in removing particulate water from the gas stream but not in removing water vapor.

Several authors (5, 6) have used the Bain circuit to measure $\dot{V}_{CO_2}$ but failed to show the reliability of the technique. The method has not previously been used to measure $\dot{V}_{O_2}$. In our study $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ measured on the Bain circuit were compared with values obtained by the non-breathing technique under similar blood gas tensions and were found to correlate closely. Nitrous oxide uptake by patients consists of two exponential phases, a rapidly changing phase lasting approximately 60 minutes followed by a slow constant phase (9). Therefore, our method is more precise during the slow phase.

As all sampled gases were returned to the circuit after gas analysis, the measuring system permitted continuous on-line studies. The 1-L anesthesia bag produced a thoroughly mixed expired gas sample as shown by the steady CO_2 concentration in the gas emerging from the bag (Fig 4, C). Eliminating the bag from the measuring system caused a slightly inhomogeneous mixture at the analyzers (Fig 4, B). If an oxymeter with a higher resolution had been available (such as the Beckman OM 11 analyzer), we could have dispensed with the recorder which we used to improve resolution.

REFERENCES

1. Ergbuth PH, Bergmen NA. The effect of a single dose of succinylcholine on oxygen consumption and carbon dioxide production in man. Anesthesiology 1973;39:447–9.
2. Noe FE, Whitty AJ, Davies KR, Wickham BL. Noninvasive measurement of pulmonary gas exchange during general anesthesia. Anesth Analg 1980;59:263–9.
3. Kennel EM, Andrews RW, Wollman H. Correction factors of nitrous oxide in the infrared analysis of carbon dioxide. Anesthesiology 1973;39:441–3.
4. Conway CM. Alveolar gas relationship during the use of semiclosed rebreathing anaesthetic systems. Br J Anaesth 1976;48:865–8.
5. Bain JA, Spoerel WE. Carbon dioxide output under anaesthesia. Can Anaesth Soc J 1976;23:153–62.
6. Greenway RE, Heeneman H, Keeri-Szanto M. Circulatory monitoring using a CO_2 analyzer during planned hypotension: a clinical study. Can Anaesth Soc J 1977;24:282–5.
7. Eger EI II. Anesthetic uptake and action. Baltimore: Williams & Wilkins Co, 1975:89.
8. Ramanathan S, Chalon J, Capan L, Patel C, Turndorf H. Rebreathing characteristics of the Bain anesthesia circuit. Anesth Analg 1977;56:822–5.
9. Barton F, Nunn JF. Totally closed circuit nitrous oxide/oxygen anaesthesia. Br J Anaesth 1975;47:350–7.

ANESTH ANALG
1982;61:366-70

Plasma Epinephrine and Norepinephrine Levels during Anesthesia: Enflurane-N_2O-O_2 Compared with Fentanyl-N_2O-O_2

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BROWN, F. F., III, OWENS, W. D., FELTS, J. A., SPITZNAGEL, E. L., JR., AND CRYER, P. E.: Plasma epinephrine and norepinephrine levels during anesthesia: enflurane-N_2O-O_2 compared with fentanyl-N_2O-O_2. Anesth Analg 1982;61: 366–70.

During intra-abdominal surgery, plasma levels of norepinephrine in peripheral venous blood were higher in 11 patients who received fentanyl-nitrous oxide-oxygen than in 10 patients who received enflurane-nitrous oxide-oxygen [703 ± 95 vs 463 ± 38 (SEM) pg/ml]. At the same time, systolic blood pressure (143 ± 6 vs 121 ± 4 torr), mean blood pressure (108 ± 4 vs 98 ± 3 torr), and pulse rate (87 ± 3 vs 98 ± 4 beats per minute) also differed significantly ($p < 0.05$); plasma levels of epinephrine (235 ± 61 vs 113 ± 21) did not. These values did not differ significantly between the two groups before induction of anesthesia, after induction but before skin incision, or in the recovery room. These data support the concept that enflurane anesthesia blocks the sympathetic response to surgical stress more effectively than low dose fentanyl anesthesia.

Key Words: ANESTHETICS, Intravenous: fentanyl; ANESTHETICS, Volatile: enflurane; BLOOD PRESSURE: hypertension; SYMPATHETIC NERVOUS SYSTEM: catecholamine, epinephrine, norepinephrine.

WE HAD THE clinical impression that systemic hypertension occurred more frequently during surgery in patients anesthetized with fentanyl-N_2O-O_2 than in patients anesthetized with enflurane-N_2O-O_2. We proposed that a greater degree of sympathetic nervous system activity would be the mechanism for the higher blood pressure during surgery in patients anesthetized with fentanyl-N_2O-O_2. First, to confirm our clinical impression and, second, to test our hypothesis for mechanism, we conducted the following study with the approval of our Human Studies Committee.

Methods

Twenty-one A.S.A. physical status I or II patients scheduled for elective intra-abdominal surgery were randomly assigned to one of two groups. Fentanyl-N_2O-O_2 was the anesthetic technique in group I; enflurane-N_2O-O_2 was the anesthetic technique in group II. Patients in both groups received diazepam, 0.1 mg/kg, orally 90 minutes before induction of anesthesia and atropine, 0.006 mg/kg, intramuscularly 20 minutes before induction of anesthesia.

Patients in group I received Innovar, 2 to 4 ml, intravenously and intravenous thiopental. Five minutes after intravenous pancuronium, 1 mg, the patients were given succinylcholine, 1.5 mg/kg, intravenously. Nitrous oxide (66%), supplemental intravenous thiopental, and incremental doses of intravenous fentanyl comprised anesthetic maintenance in group I. Intravenous pancuronium provided muscle relaxation during the operation.

Patients in group II were given intravenous thiopental for induction, the same doses of pancuronium and succinylcholine as above to facilitate intubation, 1% to 4% inspired enflurane with 50% nitrous oxide for maintenance, and intravenous pancuronium for relaxation.

All patients were ventilated mechanically. Twenty minutes after anesthesia began, an arterial blood sam-

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Supported in part by Ohio Medical Products.
Received from the Departments of Anesthesiology, Mathematics, and Medicine, Washington University, St. Louis, Missouri. Accepted for publication December 9, 1981. Presented in part at the 54th Congress of the International Anesthesia Research Society, March 10-13, 1980, Reno, Nevada.

ple was obtained from each patient to assess adequacy of oxygenation and elimination of CO_2. Neostigmine, 0.07 mg/kg IV, and atropine, 0.03 mg/kg IV, reversed the neuromuscular blockade at the end of surgery.

All patients had two intravenous lines: one for the administration of drugs and fluids, and the other, located in the opposite arm, for drawing 5-ml blood samples to measure plasma levels of norepinephrine (NE) and epinephrine (EPI). Blood samples were obtained before induction of anesthesia (base line), after induction but before the skin incision (postinduction), every 15 minutes during surgery (surgery), and at 15 and 30 minutes after arrival in the recovery room (recovery). All samples were placed in collection tubes containing glutathione and dithiothreitol, and stored in ice. Immediately after a patient's last sample, the tubes were spun in a refrigerated centrifuge and the plasma removed and frozen until the catecholamine levels were assayed at a later date. EPI and NE levels were measured by the single isotope derivative method (1).

Systolic and diastolic blood pressures were measured by sphygmomanometry and recorded each time a catecholamine blood sample was taken. Mean arterial pressure (MAP) was calculated: MAP = diastolic pressure ± ⅓ (systolic-diastolic pressure). Heart rate was recorded at the same time.

The chi-square method was used to evaluate statistical significance for sex and operation. Otherwise, the two-sample *t*-test was used. The test was two-tailed and $\alpha = 0.025$. All mean numbers reported are ± standard error of the mean. Results were considered statistically significant at $p < 0.05$.

Results

Eleven of the 21 patients were in group I. There was no statistically significant difference between groups I and II in sex (5/11 vs 6/10 female), age (47 ± 4.1 vs 39 ± 3.6 years), or weight (71.4 ± 4.3 vs 76 ± 3.8 kg). Cholecystectomy was the most common operation with eight in group I and six in group II.

Patients in group I received 4.6 ± 0.27 mg/kg of thiopental for induction and 64 ± 27 mg for supplementation. The fentanyl dose, including that in Innovar, averaged 0.33 ± 0.028 mg. The mean dose of pancuronium was 8.45 ± 0.59 mg. Duration of anesthesia was 2.09 ± 0.25 hours.

The 10 patients in group II had 4.3 ± 0.29 mg/kg of thiopental for induction and no supplemental doses. The mean pancuronium dose, 5.4 ± 0.48 mg, was significantly lower than that in group I. Anesthesia lasted 2.03 ± 0.24 hours.

Measurement of arterial blood gases revealed that patients in group I had lower mean Pa_{O_2} levels (129 ± 9 vs 188 ± 20 torr), as one would expect from the lower $F_{I_{O_2}}$. Neither arterial pH (7.42 ± 0.01 vs 7.38 ± 0.01) nor Pa_{CO_2} (35.8 ± 0.8 vs 37.3 ± 1.0 torr) differed significantly between groups I and II.

Patients had differing numbers of catecholamine determinations due to the variation in duration of anesthesia. For purposes of comparison, therefore, NE and EPI levels during surgery were derived values for each patient. The derived value was the arithmetic mean of the measured values during surgery. Data from the recovery period were analyzed in the same manner.

Venous plasma EPI levels did not significantly differ between the two groups in any of the four sampling periods (Table 1).

As shown in Table 2, venous plasma NE levels differed significantly between the two groups during surgery. Venous NE in group I was 703 ± 95 pg/ml and 463 ± 38 pg/ml in group II. NE levels did not differ between the two groups at the other sampling times.

Systolic blood pressure and mean blood pressure during surgery were significantly higher in group I than in group II (Table 3). Heart rate during surgery, on the other hand, was lower in group I than in group II (Table 3).

Discussion

These data demonstrate that during surgery venous plasma NE levels were statistically higher in patients anesthetized with low dose fentanyl-N_2O-O_2 than in patients anesthetized with enflurane-N_2O-O_2. Differing abilities of the two anesthetics to decrease the sympathetic response to surgical stress is the most likely cause of the differing levels of NE. The experimental design successfully randomized factors that might affect plasma NE, e.g., sex, age, and type of operation.

As we constructed our methodology, it was necessary to decide whether arterial or venous blood would be used for EPI and NE determinations. A review of the literature (1–13) revealed that each source is used equally, with some investigators not indicating which was used. Cryer et al (1) found that assays of EPI and NE levels from venous blood were sensitive, reproducible, and responded appropriately to both minor and major stress.

Halter et al (2) compared arterial and venous levels of EPI and NE. Arterial EPI levels were higher than

TABLE 1

Plasma Levels of Epinephrine

	Base line		Postinduction		Surgery		Recovery	
	Fentanyl	Enflurane	Fentanyl	Enflurane	Fentanyl	Enflurane	Fentanyl	Enflurane
				pg/ml				
	21	13	17	15	278	22	250	87
	25	29	24	40	55	57	132	68
	20	117	10	33	82	193	101	516
	60	17	29	13	268	165	118	283
	6	42	5	15	56	134	47	53
	42	25	35	19	251	56	157	181
	53	24	48	13	761	108	183	513
	25	21	25	8	135	68	66	172
	58	18	36	5	119	231	181	937
	49	76	19	26	360	93	583	125
	68	—	47	—	214	—	421	—
Mean	39	38	27	19	235	113	204	293
±SEM	±6	±10	±4	±4	±61	±21	±49	±89
Statistical significance	NS		NS		NS		NS	

TABLE 2

Plasma Levels of Norepinephrine

	Base line		Postinduction		Surgery		Recovery	
	Fentanyl	Enflurane	Fentanyl	Enflurane	Fentanyl	Enflurane	Fentanyl	Enflurane
				pg/ml				
	631	220	444	234	1299	370	3750	573
	166	279	236	229	527	417	959	596
	220	559	124	363	477	533	460	1885
	447	351	344	279	834	624	1330	973
	246	366	124	288	181	343	816	698
	715	325	576	187	1130	341	4290	605
	359	449	403	106	659	630	993	725
	409	125	274	192	855	541	2510	703
	798	200	414	216	657	320	1500	646
	203	368	120	265	616	509	1260	2270
	191	—	209	—	495	—	1460	—
Mean	399	324	297	236	703	463	1757	967
±SEM	±68	±40	±46	±22	±95	±38	±373	±191
Statistical significance	NS		NS		Significant		NS	

TABLE 3

Blood Pressure and Pulse Rate*

	Base line		Postinduction		Surgery		Recovery	
	Fentanyl	Enflurane	Fentanyl	Enflurane	Fentanyl	Enflurane	Fentanyl	Enflurane
Systolic blood pressure (torr)	134 ±6	139 ±10	126 ±6	120 ±7	143† ±6	121† ±4	147 ±6	147 ±9
Mean blood pressure (torr)	100 ±4	104 ±6	95 ±4	95 ±5	108.32† ±3.60	97.58† ±3.15	109 ±4	110 ±5
Pulse rate (beats/min)	79 ±3	88 ±4	80 ±2	86 ±4	87.34† ±2.98	98.35† ±4.17	78 ±5	89 ±4

* Values are means ± SEM.

† $p < 0.05$ between groups.

venous and the reverse was true for NE. Both sources reflected responses to stress. Injections of EPI were reflected in both venous and arterial samples.

Under anesthetic conditions it is not clear which, arterial or venous, source is the most appropriate for accurate samplings. We were primarily interested in changes, rather than absolute numbers, and elected to avoid potential complications of multiple arterial samplings by using venous blood.

Patients receiving fentanyl received significantly more pancuronium and N_2O than did patients anesthetized with enflurane. If pancuronium or N_2O affect plasma NE levels, one could postulate that these might have caused the higher NE levels during fentanyl anesthesia. Probably neither affected the measured NE levels in this experiment. Two studies using fluorometric techniques have examined the effect of pancuronium on plasma catecholamines. Zsigmond et al (3) found venous plasma NE levels to be essentially the same before and after intravenous pancuronium, 0.09 mg/kg, in eight patients who had received thiamylal. Takki and Tammisto (4), in a study of seven patients receiving fentanyl-N_2O-O_2 anesthesia, demonstrated that 0.1 mg/kg of intravenous pancuronium had no appreciable effect on venous plasma levels of EPI and NE.

The effects of N_2O on plasma NE and EPI levels have also been studied twice while investigating the cardiovascular effects of N_2O. Both studies used fluorometric techniques to measure catecholamines. Eisele and Smith (5) administered 40% N_2O to six volunteers for 40 minutes. No significant changes from control arterial levels of NE and EPI occurred. Smith et al (6) added 70% nitrous oxide for 15 minutes to basal halothane-O_2 anesthesia in eight volunteers. Plasma NE levels from an unstated source increased from 0.864 ± 0.155 μg/L to 1.186 ± 0.143 μg/L, a statistically significant change.

Applying the previous N_2O results to our data is difficult. The study by Smith et al (6) did not address the possibility that the acute changes associated with 70% N_2O administration were transient. At most, it appears that 40% N_2O probably has no effect and 70% N_2O may have some effect on plasma levels of NE. It is doubtful that the modest difference in N_2O concentration in our study had any appreciable effect on plasma NE levels. This belief is supported by the lack of difference in NE levels during the postinduction phase of our study.

The sensitivity of the fluorometric method used in many of the preceding studies is low (7) which impairs the ability to detect real but relatively small changes in catecholamine levels. We used the more sensitive isotope derivative technique.

Pulse rate and arterial blood pressure changed in opposite directions in the two groups during surgery. Consequently, the calculated pulse pressure product was never significantly different in the two groups. Therefore, one cannot conclude from our data that one technique is more beneficial than the other with regard to the myocardial work load or myocardial oxygen consumption.

Halter et al (8) measured arterial plasma EPI and NE levels by a double-isotope derivative enzymatic assay in eight unpremedicated patients undergoing abdominal surgery. Anesthetic maintenance consisted of 0.5% to 1.5% inspired halothane and 50% N_2O. They found that plasma levels of both EPI and NE were higher during surgery and in the recovery room than before induction of anesthesia. Our experimental design was similar to theirs. We found that all changes in EPI levels in both groups, compared with base line values, were significant except in the postinduction period. There was no significant difference in EPI level changes between the two groups in any sampling period.

All NE changes, in both groups, compared with base line values, were significantly different. The NE differences were significant between the two groups only in the surgery sampling period.

Stanley et al (9) documented that intravenous fentanyl, 24 μg/kg, prevented increases in arterial levels of cortisol, EPI, and NE during intubation; additional fentanyl to 75 μg/kg caused decreases in these hormones during surgical stimulation before cardiopulmonary bypass. Kono et al (10) studied the stress response during high dose fentanyl-N_2O-O_2 anesthesia. Their total dose of fentanyl was 100 μg/kg and, at this dose, fentanyl successfully attenuates the hormonal stress response to surgery. On the other hand, Hicks et al (11), using 15, 30, and 50 μg/kg doses of fentanyl with oxygen, found that the catecholamine response suggests either a dose-related or time-related effect of fentanyl. Our data lend further credence to the suggestion that NE levels during surgery under fentanyl anesthesia may be dose dependent.

However, our anesthetic goals differed from those of Stanley et al (9) and Kono et al (10). We chose a lower dose level of fentanyl that would allow us, in most cases, to extubate our patients in the operating room and move them to the recovery room without ventilatory support. Additional goals were alertness with some analgesia. The dosage used met these requirements.

We have demonstrated that, at this dose level of fentanyl, venous catecholamine levels were significantly increased during surgical stimulation. However, the responses of pulse and blood pressure to that increase were relatively modest. In A.S.A. physical status class I and II patients, such as the subjects of this study, we cannot show that the changes were of a serious magnitude.

REFERENCES

1. Cryer PE, Santiago JV, Shah S. Measurement of norepinephrine and epinephrine in small volumes of human plasma by a single isotope derivative method: response to the upright position. J Clin Endocrinol Metab 1974;39:1025–9.
2. Halter JB, Pflug AE, Tolas AG. Arterial-venous differences of plasma catecholamines in man. Metabolism 1980;29:9–12.
3. Zsigmond EK, Matsuki A, Kothary SP, et al. The effect of pancuronium bromide on plasma norepinephrine and cortisol concentrations during thiamylal induction. Can Anaesth Soc J 1974;21:147–52.
4. Takki S, Tammisto T. Effect of pancuronium and tubocurarine on plasma catecholamines. Ann Chir Gynaecol Fenn 1973;62: 260–4.
5. Eisele JH, Smith NT. Cardiovascular effects of 40 percent nitrous oxide in man. Anesth Analg 1972;51:956–63.
6. Smith NT, Eger EI, Stoelting RK, et al. The cardiovascular and sympathomimetic responses to the addition of nitrous oxide to halothane in man. Anesthesiology 1970;32:410–21.
7. Dobkin AB, Byles PH, Arandia HY, et al. Comparative metabolic responses to halogenated anaesthetics. Acta Anaesthesiol Scand 1972;16:69–75.
8. Halter JB, Pflug AE, Porte D. Mechanism of plasma catecholamine increases during surgical stress in man. J Clin Endocrinol Metab 1977;45:936–44.
9. Stanley TH, Berman L, Green O, et al. Plasma catecholamine and cortisol responses to fentanyl-oxygen anesthesia for coronary-artery operations. Anesthesiology 1980;53:250–3.
10. Kono K, Philbin DM, Coggins CH, et al. Renal function and stress response during halothane or fentanyl anesthesia. Anesth Analg 1981;60:552–6.
11. Hicks HC, Mowbray AG, Yhap EO. Cardiovascular effects of and catecholamine responses to high dose fentanyl-O_2 for induction of anesthesia in patients with coronary artery disease. Anesth Analg 1981;60:563–8.
12. Gothert M, Wendt J. Inhibition of adrenal medullary catecholamine secretion by enflurane. Anesthesiology 1977;46:400–3.
13. Roizen MF, Forbes AR, Miller RD, et al. Similarity between effects of pancuronium and atropine on plasma norepinephrine levels in man. J Pharmacol Exp Ther 1979;211:419–22.

Pain Relief after Thoracotomy

In a randomized controlled trial carried out during the first two days after thoracotomy, patients who had had intercostal nerves frozen with a cryoprobe or were given morphine by continuous intravenous infusion had significantly less pain at rest than patients given intramuscular morphine. Fifteen patients were assigned to each group. Differences between the groups with respect to pain on movement and during physiotherapy were not significant. Pain was estimated using visual analogue scales, and an arc sine transformation was carried out on values obtained from these scales before comparison using an analysis of variance. The trial did not distinguish between the cryoprobe and infusion treatments. The simplicity of the cryoprobe had much to commend it, but in units without access to this equipment morphine infusion offers a satisfactory alternative. *(Orr IA, Keenan DJM, Dundee JW. Improved pain relief after thoracotomy: use of cryoprobe and morphine infusion. Br Med J 1981;283:945–8)*

REVIEW
article

Anesthesia and Hypothyroidism: A Review of Thyroxine Physiology, Pharmacology, and Anesthetic Implications

John M. Murkin, MD*

DURING THE PRACTICE of clinical anesthesia, it is not uncommon to encounter patients with varying degrees of hypothyroidism, ranging from those who have been rendered essentially euthyroid by treatment with exogenous supplements, to those with overt myxedema. Despite the relative frequency of this condition, there is, however, little current information in the anesthesia literature regarding either the abnormal physiology found in hypothyroidism or the duration of treatment required for its reversal (1).

Although the incidence of perioperative morbidity associated with undiagnosed or untreated hypothyroidism is unknown, major complications have been reported (2). These included severe hypotension (3–7) or cardiac arrest (3) following induction of anesthesia, extreme sensitivity to narcotics and anesthetics with prolonged unconsciousness (4, 8), and hypothyroid coma following anesthesia and surgery (6, 7).

This review briefly discusses thyroid physiology and regulation and examines some of the biochemical, metabolic, and pharmacologic derangements that can occur. Assessment of the adequacy of thyroid replacement therapy, as well as the time course for reversal of hypothyroidism, are also considered. Finally, the anesthetic management of the hypothyroid patient is discussed to define optimal management of those patients at greatest risk.

Incidence

It has been variously estimated that 0.5% (9) to 0.8% (10) of the total adult population are hypothyroid as shown by elevated serum levels of thyroid-stimulating hormone (TSH) or decreased serum thyroxine (T_4) levels. Treated hypothyroidism has a greater prevalence in females (1.4% to 1.9%) than in males (0.1%) (10) and similarly, undiagnosed hypothyroidism has an incidence in females (0.2% to 0.3%) that is 10 times greater than in males (10, 11).

Iatrogenic hypothyroidism accounts for the majority of cases. Forty to fifty percent of thyrotoxic patients treated surgically or with radioactive iodine develop hypothyroidism within 10 years (12). Less than 30% of patients remain euthyroid following thyroidectomy (13) usually because replacement therapy has either been discontinued (15%) or is inadequate (54%) (14).

Thyroid Physiology

Thyroid Hormone Synthesis

Normal thyroid function requires an average daily intake of 100 μg of dietary iodine. Inadequate dietary iodine causes an increased secretion of TSH, with resultant thyroid hypertrophy producing a parenchymatous goiter. Iodine supplementation has largely eliminated endemic goiter in most areas.

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The thyroid gland normally contains an estimated 5000 to 7000 μg of organic iodine, which is primarily bound to thyroglobulin (15). This pool acts as a buffer to counter acute decreases in thyroid hormone synthesis so that even complete suppression of thyroid hormone synthesis for up to 2 weeks results in only a small decrease in protein-bound iodine, no change in plasma levels of TSH (16), and a normal secretion rate of 90 μg of T_4 daily.

Synthesis of thyroid hormone involves four steps: (*a*) uptake of iodine into the thyroid gland, (*b*) iodination of thyroglobulin, (*c*) coupling of iodotyrosines to form iodothyronine, and (*d*) release of thyroid hormones.

Uptake of Iodide. Dietary iodine is reduced in the intestine to its ionic form and enters the circulation as iodide. The thyroid gland is one of several organs, including the mammary gland, placenta, and skin, capable of concentrating iodide. Through an active transport mechanism a large concentration gradient is maintained with a normal ratio of thyroid to plasma iodide of 20:1. With stimulation this ratio can exceed 100:1. The transport mechanism involved is stimulated by TSH-mediated activation of adenylate cyclase (17) and can be inhibited by various ionic moieties including perchlorate and thiocyanate (hypothyroidism has been reported following prolonged sodium nitroprusside infusion) (18), as well as by excessive intracellular iodide levels.

Iodination of Thyroglobulin. Upon entering the thyroid follicular cell, iodide is acted upon by a heme-containing peroxidase to produce oxidized iodine-free radicals. These then combine with the tyrosine residues on thyroglobulin, a high molecular weight glycoprotein synthesized by the follicular cells, to produce monoiodotyrosine and diiodotyrosine.

Coupling of Iodotyrosines. Oxidative coupling of a monoiodotyrosine and a diiodotyrosine residue to form triiodothyronine (T_3), or coupling of two diiodotyrosine residues to form T_4, proceeds intracellularly and the resultant iodothyronine-thyroglobulin complex is stored extracellularly in the lumen of the thyroid follicle. These reactions, catalyzed by the same peroxidase responsible for the initial iodotyrosine formation, can be inhibited by antithyroid agents of the thioamide type including propylthiouracil, methimazole, and carbimazole, which not only inhibit iodothyronine formation but also impair initial iodide oxidation.

Release of Thyroid Hormones. By a process of endocytosis, the iodothyronine-thyroglobulin complex stored in the follicular lumen is moved intracellularly where hydrolysis by lysozymal proteolytic enzymes produces T_3 and T_4. Normally T_3 and T_4 are secreted in daily amounts approximating 8 μg and 90 μg, respectively. High intrathyroidal levels of iodide acutely inhibit thyroid hormone release by impairing the endocytosis of colloid, proteolysis, and thyroid hormone secretion. Sodium iodide is thus useful in the preoperative preparation of thyrotoxic patients. Lithium similarly inhibits thyroid hormone secretion and can produce goitrous hypothyroidism in patients treated with this agent (19).

Thyroid Hormone Regulation

The major regulator of thyroid function is TSH secreted from the anterior pituitary. Release of TSH can be stimulated in vitro by cyclic adenosine monophosphate (AMP), theophylline (inhibiting breakdown of cyclic AMP), or epinephrine (stimulating formation of cyclic AMP), which suggests a major role in vivo for cyclic AMP in pituitary activation (20).

Specific TSH receptor sites have been identified on the thyroid cell membrane (21) coupled to membrane-bound adenylate cyclase (17), the enzyme responsible for cyclic AMP formation. TSH receptor stimulation thus increases cyclic AMP formation. This activates protein kinase which phosphorylates various regulatory proteins, thus altering their function. Ultimately this results in augmented iodide uptake and increased T_3 and T_4 synthesis and secretion.

Pituitary TSH release is initiated from the ventromedian hypothalamus by thyrotropin-releasing hormone (TRH). TRH is carried from the hypothalamus to the anterior pituitary via the hypophyseal portal venous system. Hypothermia in both the rat (22) and in the human infant (23) augments TRH release from the hypothalamus. Hypothermia-induced TRH release, through TRH-mediated increases in T_3 and T_4 secretion, elevates the basal metabolic rate (BMR) to counter decreases in core body temperature. In the rat TRH release is blocked by various agents including atropine and diethyl ether (24), and these agents may thus contribute to the hypothermia seen under anesthesia in hypothyroid man (4). Increased levels of circulating T_4 (25) act in a negative feedback manner to suppress pituitary TSH release and thus allow fine control of plasma levels of T_3 and T_4.

Thyroid Hormone Transport and Metabolism

Circulating T_3 and T_4 are more than 99% bound to serum proteins (15), especially thyroxine-binding globulin (TBG) and thyroxine-binding prealbumin

(TBPA). As it is the free thyroid hormone that is biologically active, it is therefore the ratio of free hormone to bound hormone rather than the total serum concentration that determines the level of metabolic activity.

Extrathyroidal tissue stores contain approximately 900 μg of T_4 and 50 μg of T_3 (15). Plasma protein binding accounts for 50% of this, and rapidly equilibrating tissues such as liver and kidney account for the majority of the rest. Because of the relatively large size of the extrathyroidal T_4 tissue pool, and as less than 1% of the available TBG thyroxine-binding sites are occupied, an intravenous bolus injection of levothyroxine (*l*-thyroxine, L-T_4) will be rapidly redistributed into this storage pool to maintain a lower, more stable plasma level. In contrast, a bolus injection of liothyronine (L-T_3) may well exceed the capacity of its tissue stores, producing transiently high plasma levels of T_3. This can result in excessive cardiovascular and peripheral tissue stimulation resulting in angina, arrhythmias, or even sudden death (26). L-T_4 is therefore currently recommended even for treatment of hypothyroid coma as it is less likely to be associated with excessive cardiovascular stimulation (2, 6, 27).

In peripheral tissues T_4 is monodeiodinated to T_3 (28), which is considered the principal metabolically active hormone (29). Up to 75% of circulating T_3 is derived in this fashion rather than through secretion from the thyroid gland (30). T_4 is eliminated slowly from the body with a half-life of 7.5 days (14), 20% to 40% being eliminated in the stool after conjugation in the liver, whereas the majority is metabolized peripherally to T_3 (31).

At the cellular level, T_3 binds to cell nuclei (32) causing rapid incorporation of labeled nucleic acid precursors into nuclear ribonucleic acid (RNA) (33) with consequent increases in new protein synthesis and oxygen consumption. These effects of T_3 can be blocked by inhibition of protein synthesis (34), and there is a strong direct correlation between the degree of nuclear binding of T_3 and its calorigenic effect in various tissues. Spleen, testes, and brain do not increase oxygen consumption in response to T_3 administration (35). These organs have few nuclear binding sites for T_3, whereas tissues such as liver, kidney, heart, and anterior pituitary, with many T_3 nuclear receptors, are T_3 responsive (36).

An increase in both intracellular concentration and activity of sodium-potassium adenosine triphosphatase (ATPase) has been measured in T_3-treated rat hearts (37). It is felt that this may represent a major effect of T_3 on cellular metabolism. The release of energy from the increased breakdown of adenosine triphosphate (ATP) components generates heat, whereas the decrease in ATP concentration stimulates oxidative phosphorylation to produce an increase in the BMR in the intact organism. T_3 also increases mitochondrial mass and cytochrome content, thus increasing the capacity for oxidative metabolism without the uncoupling of oxidative phosphorylation (38).

Systemic Manifestations of Thyroid Deficiency

The protean systemic manifestations of hypothyroidism in humans have been recently well detailed in both the adult (14, 15) and the neonate (39). Therefore, only a brief synopsis of the clinical features of hypothyroidism is now presented, and only those areas of direct import in clinical anesthesia in the adult are discussed in detail.

"The symptoms of hypothyroidism can include dry skin, constipation, fatigue, cold intolerance, hoarseness, menorrhagia, and impairment of memory. Physical examination may disclose hoarseness, periorbital edema, lateral thinning of the eyebrows, brittle hair, dry skin, goiter, hypothermia, bradycardia and prolongation of the relaxation phase of the deep tendon reflexes" (2).

"Myxedema coma is the end stage of neglected or undiagnosed hypothyroidism characterized by cachexia, progressive stupor ending in a comatose state, hypothermia, hypoventilation and respiratory acidosis, low serum sodium and high serum lactate levels, inappropriate secretion of antidiuretic hormone, hypoglycemia, severly disordered cerebral metabolism shock and death" (40).

In primary hypothyroidism, the degree of elevation of serum TSH is generally thought to correlate with the severity of the disease (14, 41, 42). This correlation may not be absolute however, as some patients with primary hypothyroidism may have been found with serum TSH levels within the euthyroid range (43). Hypothyroidism can nevertheless be graded into subclinical (mean basal TSH, 11.2 μU/ml), mild (mean basal TSH, 17.9 μU/ml), and overt (mean basal TSH, 91.0 μU/ml) based on clinical and biochemical findings (44).

Patients with subclinical hypothyroidism are asymptomatic and have normal levels of serum T_4. TSH levels are only marginally elevated but increase disproportionately in response to exogenous TRH (45). Mild hypothyroidism may cause minor and nonspecific symptoms such as fatigue, hair loss, or con-

stipation, and these patients have T_4 levels that are low-normal but show elevated basal levels of serum TSH. In patients with overt hypothyroidism, T_4 serum levels are markedly depressed and greatly elevated levels of TSH are seen. These patients generally demonstrate obvious clinical manifestations of hypothyroidism but may occasionally appear euthyroid when the hypothryoidism has been profound but of brief duration as may occur after thyroidectomy (3) or discontinuation of thyroid medications (4).

Metabolic Rate

In overt hypothyroidism the BMR is only 55% to 60% of normal (15). This is due to a decrease in both the content and activity of mitochondrial enzymes producing a general slowing of substrate oxidation. The result is a decreased ability to increase core temperature in response to low temperature stress (45), rendering the hypothyroid patient particularly susceptible to intraoperative and postoperative hypothermia (4).

Administration of a single intravenous bolus of T_4 produces a peak increase in BMR 10 to 12 days after its administration (46). This delayed onset presumably represents monodeiodination of T_4 to T_3, hormonal binding, metabolic transformation, and protein synthesis necessary before maximal metabolic response can occur. In contrast, an intravenous bolus of T_3 produces an abrupt peak increase in BMR within 36 to 72 hours (46).

Cardiovascular System

In the myocardium, histologic changes associated with hypothyroidism may include diffuse interstitial vacuolations containing mucopolysaccharide and proteinaceous deposits. Protein and mucin-rich pericardial effusions are also frequent, being found in up to 60% of overtly hypothyroid patients (47). However, because of its gradual development, cardiac tamponade is infrequent (48).

Depression of myocardial function in hypothyroidism is evidenced by abnormal systolic time intervals. The degree of prolongation of the preejection period and the reduction of left ventricular ejection time correlate directly with the severity of clinical hypothyroidism (41). Patients with overt hypothyroidism may have a decrease in left ventricular ejection time to 60% of normal values, whereas preejection period may be prolonged by as much as 40% (41, 47). Cardiac output may decrease in overt hypothyroidism by as much as 40%, due to both a reduction in heart rate and stroke volume (49), and, combined with increased peripheral vascular resistance and decreased blood volume, results in a prolongation of the circulation time and narrowing of the pulse pressure. Although hypothyroidism per se is not believed to cause heart failure (14, 50), the associated myocardial impairment implies a decreased ability to respond to further circulatory stresses.

Myocardial depression may be partly due to myxedematous infiltration and structural disintegration occurring in severe hypothyroidism, but it is also thought to reflect impaired cellular metabolism resulting from a lack of thyroid hormone activity. It is not thought to be due to a decreased cardiovascular sensitivity to catecholamines (51). Alterations is sarcoplasmic reticulum function and depression of myosin ATPase activity contribute to the depressed myocardial contractility seen in hypothyroidism. A decrease in both the rate of calcium uptake and calcium-dependent ATP hydrolysis has been demonstrated in myocardial sarcoplasmic reticulum of hypothyroid rabbits (52). This reduction in calcium transport may be involved in the prolonged contraction characteristic of hypothyroid cardiac muscle.

Cardiovascular responses to acute increases in intrathoracic pressure are also abnormal in overtly hypothyroid patients. There is an absence of both the usual reflex slowing of heart rate, and loss of the compensatory increase in diastolic arterial pressure following a Valsalva maneuver (50). This implies a defect in the baroreceptor responses. Baroreceptor dysfunction may contribute to the tendency of hypothyroid patients to become hypotensive in response to a variety of anesthetic agents (3–7).

The electrocardiogram (ECG) in overt hypothyroidism may show flattening or inversion of the T wave in lead II, low amplitude of P, QRS, and T waves, and sinus bradycardia (53). Atrial cells in vitro from hypothyroid rabbits have a decreased rate of diastolic repolarization and prolonged duration of the action potential which may partly explain the bradycardia associated with hypothyroidism (54).

Respiratory System

Abnormalities of respiratory function, including a decrease in maximal breathing capacity and a diminished diffusing capacity for carbon monoxide, have been described in overt hypothyroidism and have been shown to improve significantly with replacement therapy (55). Hypoxic ventilatory drive may be less than 14% of normal values, showing almost no in-

crease in minute ventilation even at an alveolar oxygen tension of 40 torr (56). Hypercapnic ventilatory drive is also significantly depressed in overt hypothyroidism to less than 37% of normal values (56).

Discontinuation of L-T_4 therapy for 21 days in patients who are otherwise euthyroid while on L-T_4 replacement can elevate mean serum TSH levels to 131 μU/ml while depressing both hypoxic and hypercapnic respiratory drives to less than 50% of control values (56). Respiratory failure can thus be present either spontaneously or may follow administration of respiratory depressants (3, 8).

Sympathoadrenal System

There is evidence of increased sympathetic nervous system activity occurring in hypothyroidism in both animals and man. Increases have been demonstrated in the turnover and biosynthesis of cardiac norepinephrine in hypothyroid man (57), as well as an enhanced adrenal medullary response to hypoglycemia in hypothyroid rats (58). An increase in the ratio of alpha-adrenergic to beta-adrenergic receptors in various tissues, including atrium and aorta, due to an increase in alpha receptors, has been demonstrated in thyroidectomized rats (59). It is postulated that adrenergic receptors undergo a reversible allosteric change from alpha-receptor to beta-receptor forms that is mediated by thyroid hormone (59). The significance of this in human subjects is unclear, however, as changes in adrenergic receptor type would imply a differential sensitivity to catecholamines depending on the thyroid status of the patient (60).

Patients with thyroid dysfunction were formerly thought to have abnormal responses to catecholamines. The hyperdynamic circulatory state of hyperthyroidism was thought to result from increased sensitivity to catecholamines, whereas hypothyroid patients were felt to exhibit decreased cardiovascular sensitivity to catecholamine stimulation (61). More recent evidence, however, has not shown any change in cardiovascular responsiveness to catecholamines; today it is generally agreed that sensitivity to exogenous catecholamines is not altered by thyroid dysfunction (51, 62).

Other

Hypothyroid patients have plasma volumes 10% to 24% below normal values (63), increases in total body extracellular water (15), and varying degrees of hyponatremia (64). It is felt that the interstitial mucopolysaccharide depositions characteristic of myxedema "exert sufficient colloid osmotic pressure to oppose that of plasma protein and so lead to a transfer of saline from plasma to the interstitial fluids . . . This accounts for the peculiar clinical characters of myxedematous swellings and for the low total volume and high protein content of the plasma in this disease" (65). Also, impairment of free water excretion contributes to the hyponatremia because of changes in renal hemodynamics, with decreases in glomerular filtration rates and in creatinine clearance, as well as reductions in tubular transport (66). Inappropriate secretion of vasopressin has also been demonstrated (67). These changes give rise to postoperative fluid and electrolyte imbalances (3, 68), and similarly, the impaired renal function may be of consequence in drug elimination. Elimination of digoxin is a particular problem, as serum levels have been found to be elevated due to its impaired excretion in hypothyroid subjects (69).

Gastrointestinal hemorrhage has been reported in hypothyroidism (70) and is probably due to both increased capillary fragility as well as reductions in coagulation factors VIII and IX (71).

As many as 80% of patients with primary hypothyroidism could have elevated levels of serum cholesterol. This is mainly due to decreases in both the fecal excretion of cholesterol and its conversion to bile acids (14). Elevated serum cholesterol level is suggestive but not diagnostic of primary hypothyroidism.

Assessment of Thyroid Status

The clinical signs and symptoms of hypothyroidism are notoriously nonspecific. The only physical findings whose presence has a high statistical correlation with hypothyroidism are delayed ankle reflexes, a husky voice, and the presence of a dry skin (14). Clinical suspicions should be confirmed by measurement of serum T_4 and TSH levels, which will be diagnostic in more than 90% of subjects with either subclinical or overt hypothyroidism (72). Especially useful is radioimmunoassay of TSH levels, a method sensitive enough to detect elevated serum levels of TSH in subclinical hypothyroidism, before the patient has symptoms and before any other measurable disturbance of thyroid function (9). Normal or low serum levels of TSH in a hypothyroid patient almost always indicate secondary hypothyroidism due to hypothalamic or pituitary pathology (14). A recently developed assay for unbound serum thyroxine may prove to be the most sensitive test for the diagnosis of hypothyroidism, but it is not yet widely available clinically (43).

The TRH stimulation test, which assesses pituitary sensitivity to exogenous TRH, is of value in patients with borderline or minimal elevations of basal TSH (45). Euthyroid patients double their basal serum TSH levels within 20 to 45 minutes after intravenous TRH administration. In comparison, an absent response is found in hyperthyroid patients whereas an excessive response occurs in patients with subclinical hypothyroidism. This test may also help differentiate hypothalamic from pituitary disease in secondary thyroid dysfunction. Basal TSH is inappropriately low or undetectable in both conditions, but elevation in response to exogenous TRH indicates a hypothalamic origin for the disease. Similarly, absence of a TRH-provoked increase in TSH characterizes pituitary hypothyroidism.

Serum T_4 concentration determined by radioimmunoassay measures both protein-bound (TBG, TBPA) and unbound serum T_4. Increases in TBG concentration are often associated with conditions producing elevated estrogen levels, as occur in pregnancy, oral contraceptive administration, or hepatic cirrhosis, and may produce results at variance with the clinical assessment of the patient, i.e., a normal serum T_4 level in an apparently hypothyroid individual. Calculation of the free thyroxine index corrects for changes in TBG concentration by measuring T_4 resin uptake, which is decreased disproportionately in hypothyroidism because of increased availability of TBG-T_4 binding sites (72).

Although T_4 serum levels usually decrease before T_3 in primary hypothyroidism (72), an isolated case of T_3 myxedema coma has been described wherein T_3 levels were greatly depressed despite elevated levels of serum T_4, due to a failure of the peripheral monodeiodination of T_4 to T_3 (73).

Thyroid Replacement Therapy

Thyroid hormone replacement is most often accomplished using synthetic liothyronine (L-T_3) or *l*-thyroxine (L-T_4). Formerly, desiccated animal thyroid (thyroid USP) was utilized in dosages of 120 to 180 mg daily but this has largely been abandoned due to problems of product standardization (42). Approximate therapeutic equivalences of L-T_4 and L-T_3 are 100 μg and 25 μg, respectively (14). In most patients, L-T_4 is considered more efficacious (74), as L-T_4 has a long half-life (7.5 days) and more gradual onset of action (onset of action in 6 to 12 hours with a peak metabolic effect occurring after 10 to 12 days) than L-T_3 (60). Furthermore, the large extrathyroid tissue pool and slow turnover rates of L-T_4 protect against lapses in intake, with resulting serum and tissue levels that are more constant.

The recommended maintenance dose of L-T_4 was formerly 200 to 400 μg/day, as higher than normal serum thyroxine levels were considered necessary to compensate for the lack of metabolically active T_3 in athyreotic subjects (14). It has now been established that L-T_4 is converted in the peripheral tissues to T_3, and more recent data indicate that a dosage of 150 to 200 μg of L-T_4 is sufficient to maintain a clinically euthyroid state and to lower elevated TSH levels into the normal range (75).

One acceptable dosage protocol in older patients or those with cardiac disease is L-T_4, 25 μg/day, increasing monthly by 25-μg increments until a euthyroid state is achieved (2, 14). Younger patients, or those with less risk of myocardial disease, may start L-T_4 therapy with 50 μg/day and increase by 50 μg monthly. The first evidence of a response to therapy in hypothyroidism is a sodium and water diuresis and a decrease in serum levels of TSH which stabilizes within 4 to 6 weeks of each dosage change (14).

The route, rate, and manner of thyroid replacement therapy are determined primarily by the clinical status of the patient. The hazards of initiation of thyroid replacement therapy in patients with overt hypothyroidism and ischemic heart disease are well known. In these patients full thyroid supplementation frequently exacerbates angina or may precipitate myocardial infarction. This often necessitates acceptance of incomplete control of hypothyroidism, often in spite of the addition of coronary vasodilators and beta blocking agents (76).

Coronary revascularization has been proposed for overtly hypothyroid patients who are unable to tolerate thyroid replacement because of incapacitating angina (68, 76, 77). In one series of six patients with severe ischemic heart disease and untreated overt hypothyroidism (mean TSH $>$ 100 μU/ml) two patients received either 25 μg of L-T_4 daily or 7.5 mg of thyroid USP before coronary artery bypass surgery but died suddenly before coronary revascularization (77). Of the remaining four patients, one received no thyroid medication, and three received 50 μg or less of L-T_4 per day before surgery, but all underwent successful coronary bypass surgery and were subsequently able to tolerate full thyroid replacement therapy (77). In a similar report, two patients with overt hypothyroidism successfully underwent heart catheterization and coronary revascularization without any preoperative thyroid replacement therapy (68). One

of these patients, however, remained without thyroid supplements 6 days after surgery and subsequently developed inappropriate vasopressin secretion and adynamic ileus requiring prolonged hospitalization for 2½ months. Both of these problems are recognized complications of untreated overt hypothyroidism (3). A third patient who was given L-T_3 before surgery, in doses that were increased gradually to 25 μg daily, died suddenly following severe chest pain before surgery (68).

These reports emphasize the risk of stressing an ischemic myocardium with the increased metabolic rate and circulatory demands resulting from initiation of thyroid replacement therapy. They also imply that major surgery can be undertaken successfully in severely hypothyroid patients with little or no preoperative thyroid replacement therapy. It must be realized, however, that hypothyroid patients who have coronary artery surgery not only benefit from intensive perioperative monitoring of cardiovascular, respiratory, and metabolic parameters during surgery, but also the very nature of the procedure can be expected to produce an improvement in postoperative myocardial performance (77).

In the absence of apparent ischemic heart disease most authors advocate preoperative thyroid supplements (2, 12, 43, 78), in a dosage of 150 μg of L-T_4 daily (43), to minimize the risk of profound postoperative central nervous system (CNS) depression, facilitate recovery from surgical stress, and promote wound healing (43).

In extreme cases, e.g., myxedema coma, the use of L-T_3 in the extremely small dose of 5 μg in the first 24 hours has been advocated (12), recognizing that angina and sudden death have been recorded following a single dose of 50 μg (26). Alternatively, 300 to 500 μg of L-T_4 by slow intravenous infusion, followed by 50 to 100 μg/day, can be used (78) and may have lesser potential for production of acute myocardial stress (79).

Reversal of Systemic Changes in Hypothyroidism

Exogenous replacement therapy can completely reverse the systemic manifestations of hypothyroidism, but the time course varies with both the degree and the duration of the disease, and the system involved.

Skeletal muscle biopsies from patients with overt hypothyroidism may demonstrate hypothyroid myopathy, showing type II muscle fiber atrophy and greatly increased numbers of central muscle fiber nuclei (80). The severity of the myopathy is proportional to the degree of hypothyroidism as assessed clinically and biochemically, and is particularly related to the degree of elevation of levels of serum TSH (81). Complete reversal of hypothyroid myopathy may not occur until long after other stigmata of overt hypothyroidism have regressed. Patients with long-standing hypothyroidism may still have weakness and abnormal muscle biopsy specimens 7 to 15 months after initiation of adequate replacement therapy despite normalization of serum T_3, T_4, and TSH levels (81).

Patients with hypothyroid cardiomegaly demonstrate a range of responses to thyroid replacement therapy. In one patient, as little as 25 μg of L-T_4 per day was able to reverse the myocardial impairment in 2 to 4 weeks (47). In most patients, the average dose required to produce significant improvement in myocardial performance is 100 μg of L-T_4 daily. This is attained after 2 to 4 months of replacement therapy, at which time serum T_4 and TSH levels have also normalized (47). A dosage of 150 μg of L-T_4 daily is sufficient to reverse all demonstrable myocardial impairments and also causes complete resolution of pericardial effusions (47).

A decrease in serum TSH levels parallels the improvements in myocardial performance associated with L-T_4 therapy. This implies that due to the presence of specific T_3 receptors on cell nuclei of both the anterior pituitary and the myocardium, TSH levels mirror tissue bioavailability of thyroid hormone and can accurately reflect the degree of reversal of myxedematous changes (47).

Pharmacologic Interactions

Serum Thyroxine and Drug Metabolism

T_4 in physiologic doses increases hepatic mixed function oxidase activity and so stimulates hepatic drug metabolism in rats. In particular, NADPH (reduced nicotinamide adenine dinucleotide phosphate)-cytochrome *c* reductase activity is greatly augmented (82). T_4 also produces a progressive dose-dependent decrease in hepatic cytochrome P-450 content such that excessive serum levels of T_4 cause a net depression of hepatic drug metabolism (82). In thyroidectomized rats, the content of total hepatic microsomal protein decreases by 11%, whereas the activity of NADPH-cytochrome *c* reductase decreases by 63% (83), compatible with the observation that thyroidectomy generally diminishes the rate of hepatic drug metabolism in rats (84).

In man, the half-life of antipyrine, which is largely metabolized in the liver, has been shown to parallel the degree of thyroid activity. The half-life of antipyrine is consistently prolonged in patients with hypothyroidism, shortened in patients with hyperthyroidism, and returns to the normal range only when patients are rendered euthyroid (85). Hypothyroid patients also have increased sensitivity to a variety of drugs, particularly narcotics (3, 4, 8). Morphine is largely metabolized in the liver through conjugation with glucuronic acid and, to a lesser extent, by *N*-demethylation (86). The fact that *N*-demethylation activity is greatly reduced in thyroidectomized rats (83), suggests that the increased sensitivity of hypothyroid patients to morphine may in part be related to decreased hepatic metabolism of morphine.

Influence of Anesthetics on Serum Thyroxine

The effects of various anesthetic agents on serum thyroxine levels have been reviewed by Halevy (87) and Oyama (88). In man, halothane (89), diethyl ether (90), and isoflurane (91) all increase serum T_4 levels without increasing the output of T_4 from the thyroid gland. This likely represents mobilization of bound thyroxine from peripheral tissue pools, particularly in the liver (90).

In contrast, methoxyflurane (92) and spinal anesthesia (93) have little effect, whereas nitrous oxide-thiopental anesthesia (90) decreases serum levels of T_3 and T_4. The antithyroid property of thiopental is related to its thiourylene nucleus. Thiourylene, chemically allied to thiouracil (94), inhibits peripheral deiodination of T_4 to T_3 (29).

In patients with relatively fixed rates of T_4 supply, as in either untreated hypothyroidism or patients on a fixed replacement dose of T_4, phenobarbital decreases the level of circulating T_4 by enhancing hepatic clearance and excretion (95).

MAC and Thyroid Status

The level of thyroid activity in animals has a minor effect on anesthetic requirements (minimal alveolar concentration, MAC) for halothane and cyclopropane (96, 97). In rats, altered thyroid activity has no significant effect on anesthetic requirements for cyclopropane (96). MAC values are temperature dependent, and thyroid-induced changes in MAC may be attributable to the effect of thyroid-induced changes in temperature on lipid solubility (96). The MAC of halothane in temperature-controlled dogs directly parallels the level of thyroid activity but these changes are statistically significant only at extremes of thyroid activity (97). The authors of these studies conclude that the changes in MAC due to thyroid activity are slight and would probably not be clinically apparent (96, 97).

The lack of correlation between anesthetic requirements and thyroid activity may be related to the semiautonomous nature of cerebral metabolism, which is maintained independent of thyroid activity. This has been demonstrated in brain tissue slices which show no significant change in oxygen consumption in response to thyroxine administration (35, 98).

There are no studies available on anesthetic requirements in hypothyroid man but the clinical impression that increased sensitivity to anesthetics exists in the hypothyroid state is widespread and long established (2, 99, 100). If correct, this impression does not necessarily imply a change in MAC per se, but may rather reflect an increased susceptibility to secondary effects of anesthetic agents. Decreases in cardiac output may produce a more rapid anesthetic induction with volatile agents, and combined with decreased circulating blood volumes and abnormal baroreceptor function may readily produce hypotension after onset of anesthesia. Similarly, reductions in hepatic drug metabolism and renal drug excretion, as well as depression of respiratory drive, can prolong elimination of both fixed and volatile anesthetics leading to delayed recovery from anesthesia.

Anesthetic Management

Subclinical Hypothyroidism

Subclinical hypothyroidism is diagnosed entirely by the presence of minimally elevated serum levels of TSH with normal serum levels of T_3 and T_4 (41, 44). These patients are completely asymptomatic. Elevated levels of TSH may indicate a global pituitary intracellular deficiency of thyroid hormone activity (14), but neither the frequency nor the rate of progression to overt hypothyroidism is known. Subclinical hypothyroidism maintains normal peripheral tissue function as determined from ankle tendon reflex times, serum cholestrol and triglyceride levels, and inspection of electrocardiogram (ECG) tracings (44). Myocardial function is similarly unchanged from the euthyroid state (41, 47). Subclinical hypothyroidism does not present any particular anesthetic problems although the influence of chronic phenobarbital (95) or prolonged sodium nitroprusside infusions (18) in

accelerating progression to overt hypothyroidism is unclear.

Mild Hypothyroidism

Elevations of serum TSH and low-normal serum T_4 levels characterize mild hypothyroidism (44). Fatigue, constipation, and hair loss may be present, reflecting deficient thyroid hormone activity, but no significant abnormalities of peripheral tissue or cardiorespiratory function are demonstrable. As with all cases of hypothyroidism, it is essential to exclude secondary hypothyroidism with its attendant risk of multiple endocrine failure including adrenal insufficiency and diabetes insipidus (12). Secondary hypothyroidism may be screened for by measuring serum levels of T_4 and TSH, and if necessary, by a TRH stimulation test to delineate hypothalamic from pituitary disease (14).

Mild hypothyroidism does not prelude elective surgery but L-T_4 therapy should commence before surgery at full replacement dosage of 100 to 200 μg daily in the absence of cardiac disease.

Overt Hypothyroidism

The occurrence of deranged phsyiologic and metabolic processes in overt hypothyroidism places these patients at increased risk during anesthesia and surgery. Of particular concern is the potential for precipitation of hypothyroid coma following general anesthesia (6, 7). Elective procedures are thus contraindicated in overt hypothyroidism and should be deferred until the patient has been rendered euthyroid.

In severe overt hypothyroidism, the depressed myocardial function and hypoxic ventilatory drive return to normal within 3 to 6 months on a daily maintenance dosage of 150 μg of L-T_4 (41, 47, 56). The hypometabolic state proposed to account for the decreased metabolic clearance rate of L-T_4 also returns to normal within 6 months of thyroid hormone supplementation (101). There is a general correlation between the severity of primary hypothyroidism and the degree of elevation of serum TSH levels (44). With treatment, TSH levels normalize in concert with the return of normal peripheral tissue function (47). Serial TSH levels may be used to monitor the resolution of residual hypothyroidism.

Patients with adequately treated hyothyroidism should not require any particular investigations or anesthetic regimen but if residual hypothyroidism is suspected, it may be assessed by measuring the levels of serum T_3, T_4, and TSH. Thyroid supplements may be omitted on the day of surgery if necessary, as L-T_4 has a long half-life (7½ days) and can be administered either orally or intravenously (14).

When possible, emergency surgery should be deferred for at least 48 hours after initiation of thyroid replacement therapy to allow for latent onset of thyroid hormone activity (43). As patients with myocardial ischemia are at risk of acute coronary insufficiency or infarction during initiation of thyroid hormone replacement, they should receive a low initial dosage of 25 to 50 μg of L-T_4 daily (2, 14). The main indication for urgent preoperative thyroid hormone replacement in large dosage is incipient or overt hypothyroid coma, particularly when accompanied by severe hypothermia, drug overdose, or infection (60, 78). The use of L-T_4 in a dosage of 300 $\mu g/m^2$ by slow intravenous infusion is favored (2, 60, 78). L-T_4 has an apparently greater therapeutic margin of safety than L-T_3 and need only be given once to replenish peripheral tissue stores (78). L-T_3 in a dosage of 5 μg intravenously is, however, also recommended by some (12). Large doses of thyroid hormone should only be administered during continuous ECG monitoring to detect onset of atrial or ventricular irritability (79).

Because of an increased incidence of adrenocortical insufficiency in patients with hypothyroidism (102), and as an adrenocorticotropic hormone (ACTH) response to stress is impaired in overt hypothyroidism (103), it is recommended that patients with severe overt hypothyroidism receive daily steroid coverage of 300 mg of hydrocortisone during any acute stress (2, 12, 78).

Preoperative sedation should be omitted as overtly hypothyroid patients are profoundly sensitive to narcotics (3, 4, 8) and may be somnolent and lethargic due to the depressant effect of hypothyroidism on the CNS (104).

Regional nerve blocks should be utilized when possible. The dosage of local anesthetic should be as little as feasible to avoid toxicity secondary to impaired rates of metabolism of local anesthetics. Supplemental hypnotics should be used sparingly if at all.

Because adynamic ileus, megacolon, and delayed gastric emptying are associated with severe hypthyroidism (3, 105), general anesthesia should include endotracheal intubation with cuffed tubes to secure the airway. In severe overt hypothyroidism awake intubation may be indicated (3).

Hoarseness and dysarthria can indicate myxedematous infiltrations of the tongue and vocal cords (106), whereas dysphagia may be an early manifestation of goitrous tracheal compression. This can be

assessed by studying the chest roentgenogram for evidence of tracheal narrowing or deviation.

The cardiorespiratory changes of hypothyroidism can stimulate congestive heart failure. Cardiomegaly, pleural and pericardial effusions, ascites, peripheral edema, and diffuse T-wave inversion on ECG are often seen. In hypothyroidism, however, cardiac output increases and peripheral vascular resistance decreases with exercise (107). In addition the Valsalva maneuver does not elicit the "square wave" characteristic of heart failure (108), and venous pressure is usually normal even in the presence of a pericardial effusion (48). Congestive heart failure is uncommon even in severe overt hypothyroidism (14) and may indicate preexisting cardiac disease or an unrecognized myocardial infarction (60).

Hypothyroidism, with its attendant hypothermia, produces chronic peripheral vasoconstriction resulting in significant decreases in blood volume of up to 1 L (60). Any peripheral vasodilation or further decrease in circulating volume may thus precipitate cardiovascular collapse (60). This renders hypothyroid patients particularly susceptible to hypovolemic shock. Therefore, monitoring of central venous pressure as an index of central blood volume is essential during major surgery.

The choice of induction agent should take into account possible decreases in blood volume. Cardiac arrest temporally related to injection of 200 mg of thiopental in overt hypothyroidism (3) may be attributable to a relative overdosage in this hypovolemic state. Small, incremental doses of thiopental rather than bolus injections allow a more controlled induction (4). Another potential disadvantage of thiopental is its tendency to inhibit peripheral conversion of thyroxine into triiodothyronine, although the short-term clinical significance of this is unclear.

Ketamine for induction in severe hypothyroidism has not been reported, but it may offer potential advantages over thiopental. Although ketamine produces dose-related myocardial depression in the isolated dog heart (109), a positive inotropic effect occurs in man (110). This is thought to reflect, in part, a direct action on the myocardium (110). Similarly, in the intact dog made acutely hypovolemic, ketamine maintains or slightly increases blood pressure (111) and so has been advocated for use in the presence of hypovolemia (110). In view of the generally increased sympathetic tone and augmented sympathetic response to stimuli (58), as well as an essentially normal response to exogenous catecholamines (62) in hypothyroidism, ketamine would be expected to maintain or increase blood pressure during induction even in severe overt hypothyroidism. The potential for postoperative agitation following ketamine remains unknown and would have to be assessed individually, as would its use in patients with ischemic heart disease.

Nitrous oxide and oxygen with controlled ventilation is the technique of choice for maintenance of anesthesia (3, 4, 12, 100). Potent inhalational agents for supplementation should be used cautiously as even low concentrations may produce profound hypotension and exacerbate hypothermia (3). Narcotics including fentanyl (4) or morphine (8), even in very low dosages, may be associated with prolonged recovery from anesthesia (4) or may precipitate hypothyroid coma (8). Cyclopropane has been suggested for use in hypothyroidism (3) due to its sympathoadrenal stimulation. However, the lack of availability of cyclopropane in many institutions today precludes its use in many hospitals.

Controlled ventilation should be used in such a way that hypocapnia due to decreased production of carbon dioxide does not result. Cerebral oxygen consumption is not decreased in hypothyroidism (35), in spite of decreases in cardiac ouput. Therefore, decreases in cerebral blood flow, whether induced by hypocapnia or other means, may be potentially hazardous.

The duration of action of succinylcholine appears to be normal in hypothyroid patients (4). Neostigmine preceded by atropine has been successfully used for reversal of *d*-tubocurare (3) and pancuronium (4) in patients with overt hypothyroidism.

The need for prolonged respiratory support, including intubation and ventilation, must be anticipated before surgery. Recovery from anesthesia may be substantially delayed in hypothyroid patients, and this combined with a preexisting respiratory muscle weakness (60) may be associated with hypoventilation. Caution is advised with extubation of hypothyroid patients as they may initially ventilate adequately but can subsequently develop respiratory failure due to administration of narcotics, or increasing hypothermia, or other complications (7).

Body temperature of hypothyroid patients must be continuously monitored during anesthesia and surgery. However, despite warming blankets (4) and increased operating room temperatures (3) hypothermia may still occur in hypothyroid patients. Core rewarming using warmed intravenous solutions, peritoneal lavage, and similar techniques, is indicated if body temperature falls below 32°C to avoid the dan-

ger of refractory hypothermia-induced cardiac arrhythmias (112). Surveillance and support of body temperature must be continued during the postoperative period as hypothermia increases mortality in patients with hypothyroidism (113). Passive external warming using insulating blankets may be utilized after surgery with all but severe hypothermia to avoid increased metabolic demands and hypovolemic shock due to peripheral vasodilation (60). Preoperative thyroid hormone administration should tend to minimize further decreases in core temperature (7).

Solutions containing dextrose and saline should be utilized for intravenous fluid therapy and must be closely monitored to avoid progressive hyponatremia due to impaired free water excretion. Treatment of severe hyponatremia in hypothyroid coma includes intravenous hypertonic saline, furosemide, and L-T_4 (64).

Late postoperative complications seen with overt hypothyroidism include hyponatremia (3, 68), inappropriate vasopressin secretion (68), and adynamic ileus (3, 68).

Summary

Hypothyroidism produces major derangements of normal physiology. Depression of myocardial function, decreased hypoxic and hypercapnic ventilatory responses, abnormal baroreceptor function, and reductions in plasma volume may all be present. In addition, the presence of anemia, hypoglycemia, hyponatremia, decreased free water excretion, and impaired hepatic drug metabolism may all adversely influence responses to anesthesia.

Most reported complications have occurred in patients with unrecognized hypothyroidism. Preoperative recognition of hypothyroidism is essential for the safe anesthetic management of these patients.

Elective surgical procedures should not be undertaken in the presence of untreated hypothyroidism. Thyroid supplements should be given preoperatively to hypothyroid patients before emergency surgery.

Intraoperative and postoperative hypothermia and electrolyte disturbances are relatively common and must be guarded against.

ACKNOWLEDGMENTS

The author wishes to thank Dr. P. C. Duke and Dr. D. B. Craig for their assistance in preparing this article, and Joan Bachmeyer for secretarial help.

REFERENCES

1. Boutros AR. Anesthesia and the thyroid gland: a review. Can Anaesth Soc J 1961;8:586–615.
2. White VA, Kumagai LF. Preoperative endocrine and metabolic considerations. Med Clin North Am 1979;63:1321–34.
3. Abbott TR. Anaesthesia in untreated myxoedema: report of two cases. Br J Anaesth 1967;39:510–4.
4. Kim JM, Hackman L. Anesthesia for untreated hypothyroidism: report of three cases. Anesth Analg 1977;56:299–302.
5. Catz B, Russell S. Myxedema, shock and coma. Arch Intern Med 1961;108:407–17.
6. Holvey DN, Goodner CJ, Nicoloff JT, Dowling JT. Treatment of myxedema coma with intravenous thyroxine. Arch Intern Med 1964;113:89–96.
7. Senior RM, Birge SJ, Wessler S, Avioli SV. The recognition and management of myxedema coma. JAMA 1971;217:61–5.
8. Nordquist P, Dhuner KG, Stenberg K, Orndahl G. Myxedema coma and CO_2 retention. Acta Med Scand 1960;166:189–94.
9. Evered DC, Hall R. Hypothyroidism. Br Med J 1972;1:290–3.
10. Tunbridge WMG, Evered DC, Hall R, et al. The spectrum of thyroid disease in a community, the Wickham Study. Clin Endocrinol 1977;7:481–93.
11. Gordin A, Heinonen OP, Saarinen P, Lamberg BA. Serum thyrotropin in symptomless autoimmune thyroiditis. Lancet 1972;1:551–4.
12. James ML. Endocrine disease and anaesthesia. Anaesthesia 1970;25:232–52.
13. Hedley AJ, Flemming CJ, Chesters MI, Michie W, Crooks J. Surgical treatment of thyrotoxicosis. Br Med J 1970;1:519–23.
14. Ibbertson HK. Hypothyroidism. Pharmacol Ther C 1977;2: 177–96.
15. Ingbar SH, Woebar KA. The thyroid gland. In: Williams RH, ed. Textbook of endocrinology. Philadelphia: WB Saunders, 1981:117–247.
16. Utiger RD, Radioimmunoassay of human plasma thyrotropin. J Clin Invest 1965;44:1277–86.
17. Field JB. Thyroid-stimulating hormone and cyclic adenosine 3′,5′-monophosphate in the regulation of thyroid gland function. Metabolism 1975;24:381–93.
18. Nourok DG, Glassock KJ, Solomon DH, Maxwell MH. Hypothyroidism following prolonged sodium nitroprusside therapy. Am J Med Sci 1964;248:129–38.
19. Emerson CH, Dyson WL, Utiger RD. Serum thyrotropin and thyroxine concentrations in patients receiving lithium carbonate. J Clin Endocrinol 1973;36:338–46.
20. Wilber JF, Peake GT, Utiger RD. Thyrotropin release in vitro: stimulation by cyclic 3′,5′-adenosine monophosphate. Endocrinology 1969;84:758–60.
21. Amir SM, Carraway TF, Kohn LD. The binding of thyrotropin and isolated bovine thyroid plasma membranes. J Biol Chem 1973;248:4092–4100.
22. Montoya E, Seibel MJ, Wilber JF. Thyrotropin-releasing hormone secretory physiology: studies by radioimmunoassay and affinity chromatography. Endocrinology 1975;96:1413–8.
23. Wilber JF, Baum D. Elevation of plasma TSH during surgical hypothermia. J Clin Endocrinol 1970;31:372–5.
24. Kotani M, Onaya T, Yamada T. Acute increases of thyroid hormone secretion in response to cold and its inhibition by agents which act on the autonomic nervous system. Endocrinology 1973;92:288–94.
25. Chopra IJ, Soloman DH, Chua Taco GN. Thyroxine: just a pro-hormone or a hormone too? J Clin Endocrinol Metab 1973;36:1050–7.
26. Anderson A, Hausmann W. Triiodothyronine in myxoedema coma (letter). Lancet 1956;2:999.
27. Capiferri R, Evered D. Investigation and treatment of hypothyroidism. Clin Endocrinol Metab 1979;8:39–47.
28. Schwartz HL, Surks MI, Oppenheimer JH. Quantitation of extra-thyroidal conversion of L-thyroxine to 3,4,3-triiodo-L-thyronine in the rat. J Clin Invest 1971;50:1124–30.
29. Oppenheimer JH, Schwartz HL, Surks MI. Propylthiouracil (PTU) inhibits the conversion of L-thyroxine (T_4) to L-triiodo-

thyronine (T_3) a possible explanation of the anti-T_4 effect of PTU and further support of the concept that T_3 is the primary thyroid hormone. J Clin Invest 1972;51:2493–7.
30. Surks MI, Schadlow AR, Stock JM. Determination of iodothyronine absorption and conversion of L-thyroxine (T_4) to L-triiodothyronine (T_3) using turnover rate techniques. J Clin Invest 1973;52:805–11.
31. Gilman AG, Murad F. Thyroid and antithyroid drugs. In: Goodman LS, Gilman A, eds. The pharmacological basis of therapeutics. New York: Macmillan, 1980:1397–1419.
32. Koerner D, Surks MI, Oppenheimer JH. In vitro demonstration of specific triiodothyronine binding sites in rat liver nuclei. J Clin Endocrinol Metab 1974;38:706–9.
33. Tata JR, Sidnell CC. Ribonucleic acid synthesis during the early action of thyroid hormones. Biochem J 1966;98:604–20.
34. Tata JR. Inhibition of the biological action of thyroid hormones by actinomycin D and puromycin. Nature 1963;197: 1167–8.
35. Barker SB, Klitgaard HM. Metabolism of tissues excised from thyroxine injected rats. Am J Physiol 1952;170:31–6.
36. Oppenheimer JH, Schwartz HL, Surks MI. Tissue differences in the concentration of triiodothyronine nuclear binding sites in the rat liver, kidney, pituitary, heart, brain, spleen and testis. Endocrinology 1974;95:897–903.
37. Philipson KD, Edelman IS. Thyroid hormone control of Na^+-K^+-ATPase and K^+-dependent phosphatase in rat heart. Am J Physiol 1977;196–201.
38. Nishiki K, Erecinska M, Wilson DF, Cooper S. Evaluation of oxidative phosphorylation in hearts from euthyroid, hypothyroid, and hyperthyroid rats. Am J Physiol 1978;234:212–9.
39. Fisher DA, Klein AH. Thyroid development and disorders of thyroid function in the newborn. N Engl J Med 1981;304:702–12.
40. Werner SC. Myxedema coma. In: Werner SC, Ingbar SH, eds. The thyroid: a fundamental and clinical text. New York: Harper & Row, 1978;970–3.
41. Bough EW, Crowley WF, Ridgway EC, et al. Myocardial function in hypothyroidism: relation to disease severity and response to treatment. Arch Intern Med 1978;138:1476–80.
42. Selenkow HA, Rose LI. Comparative clinical pharmacology of thyroid hormones. Pharmacol Ther C 1976;1:331–49.
43. Hellman DE. The thyroid gland. In: Brown BR, Blitt CD, Giesecke AH, eds. Anesthesia and the patient with endocrine disease. Philadelphia: FA Davis, 1980:109–44.
44. Evered DC, Ormstron BJ, Smith PA, Hall R, Bird T. Grades of hypothyroidism. Br Med J 1973;1:657–62.
45. Lamberg BA, Gordin A. Abnormalities of thyrotropin secretion and clinical implications of the thyrotropin releasing hormone stimulation test. Ann Clin Res 1978;10:171–83.
46. Blackburn CM, McConahey W, Keating FR Jr, Albert A. Calorigenic effects of single intravenous doses of L-triiodothyronine and L-thyroxine in myxedematous persons. J Clin Invest 1954;819–24.
47. Crowley WF, Ridgway EC, Bough EW, et al. Noninvasive evaluation of cardiac function in hypothyroidism: response to gradual thyroxine replacement. N Engl J Med 1977;296:1–6.
48. Marks PA, Roof BS. Pericardial effusion associated with myxedema. Ann Intern Med 1953;39:230–40.
49. Campbell JA. A correlation of clinical and hemodynamic studies in patients with hypothyroidism. J Clin Invest 1958;37: 502–10.
50. McBrien DJ, Hindle W. Myxoedema and heart-failure. Lancet 1963;1:1066–8.
51. Skelton CL, Sonnenglick LH. Cardiovascular system. In: Werner SC, Ingbar SH, eds. The thyroid: a fundamental and clinical text. New York: Harper & Row, 1978:861–7.
52. Suko J. The calcium pump of cardiac sarcoplasmic reticulum: functional alterations at different levels of thyroid state in rabbits. J Physiol (Lond) 1973;228:563–82.
53. Douglas AH, Samuel P. Analysis of electrocardiographic patterns in hypothyroid heart disease. NY State J Med 1960;60: 2227–35.
54. Johnson PN, Freedberg AS, Marshall JM. Action of thyroid hormone on the transmembrane potentials from sinoatrial cells and atrial muscle cells in isolated atria of rabbits. Cardiology 1973;58:273–89.
55. Wilson WR, Bedell GN. The pulmonary abnormalities in myxedema. J Clin Invest 1960;39:42–55.
56. Zwillich CW, Pierson DJ, Hofeldt FD, Lufkin EG, Weil JV. Ventilatory control in myxedema and hypothyroidism. N Engl J Med 1975;292:662–5.
57. Landsberg L, DeChamplain J, Axelrod J. Increased biosynthesis of cardiac norepinephrine after hypophysterectomy. J Pharmacol Exp Ther 1969;165:102–7.
58. Johnson DG. Adrenomedullary response to 2-deoxyglucose in the hypothyroid, euthyroid and hyperthyroid rat. Acta Physiol Scand 1965;65:337–43.
59. Kunos G, Vermes-Kunos I, Nickerson M. Effects of thyroid state on adrenoceptor properties. Nature 1974;250:779–81.
60. Nicoloff JT. Myxedema coma. Pharmacol Ther C 1976;1:161–9.
61. Waldenstein SS. Thyroid-catecholamine interrelations. Annu Rev Med 1966;17:123–32.
62. McDevitt DG, Riddell JG, Hadden DR, Montgomery DAD. Catecholamine sensitivity in hyperthyroidism and hypothyroidism. Br J Clin Pharmacol 1978;6:297–301.
63. Aikawa JK. The nature of myxedema: alterations in the serum electrolyte concentrations and radiosodium space and in the exchangeable sodium and potassium contents. Ann Intern Med 1956;44:30–9.
64. Shalev O, Naparstek Y, Brezis M, Ben-Yishai D. Hyponatremia in myxedema: a suggested therapeutic approach. Isr J Med Sci 1979;15:913–6.
65. Byrom FB. The nature of myxedema. Clin Sci 1933;1:273–85.
66. Emmanouel DS, Lindheimer MD, Katz A. Mechanism of impaired water excretion in the hypothyroid rat. J Clin Invest 1974;54:926–34.
67. Skowsky WR, Kikuchi TA. The role of vasopressin in the impaired water excretion of myxedema. Am J Med 1978;64: 613–21.
68. Nelson JC, Palmer FJ, Bowyer AF. The successful treatment of myxedema and coronary artery disease in patients intolerant of thyroid hormone. Med Arts Sci 1974;28:15–22.
69. Shenfield GM, Thompson J, Horn DB. Plasma and urinary digoxin in thyroid dysfunction. Eur J Clin Pharmacol 1977;12: 437–43.
70. Orr FR. Haemorrhage in myxoedema coma. Lancet 1962;2: 1012.
71. Simone JV, Abildgaard CF, Schulman I. Blood coagulation in thyroid dysfunction. N Engl J Med 1965;273:1057–61.
72. Homberger, HA, Hewan-Lowek. Predictive values of thyroxine, thyrotropin and triiodothyronine concentrations in serum. Clin Chem 1979;25:669–74.
73. Lizarralde G, Baldwin JG, McCulley HG, Packer RM. Myxedema coma and normal serum thyroxine. South Med J 1978;71:860–2.
74. Evered D, Young ET, Ormston BJ, Menzies R, Smith PA, Hall R. Treatment of hypothyroidism: a reappraisal of thyroxine therapy. Br Med J 1973;3:131–4.
75. Stock JM, Surks MI, Oppenheimer JH. Replacement dosages of L-thyroxine in hypothyroidism. N Engl J Med 1974;290: 529–33.
76. Levine HD. Compromise therapy in the patient with angina pectoris and hypothyroidism: a clinical assessment. Am J Med 1980;69:411–8.
77. Paine TD, Rogers WJ, Baxley WA, Russell RO. Coronary arterial surgery in patients with incapacitating angina pectoris and myxedema. Am J Cardiol 1977;40:226–31.

78. Urbanic RC, Mazzaferri EL. Thyrotoxic crisis and myxoedema coma. Heart Lung 1978;7:435–47.
79. Wenzel KW, Meinhold H. Evidence of lower toxicity during thyroxine suppression after a single 3 mg L-thyroxine dose: comparison of the classical L-triiodothyronine test for thyroid suppressibility. J Clin Endocrinol 1974;38:902–5.
80. McKeran RO, Slavin G, Andrews TM, et al. Muscle fibre type changes in hypothyroid myopathy. J Clin Pathol 1975;28:659–63.
81. McKeran RO, Ward P, Slavin G, Paul EA. Central nuclear counts in muscle fibres before and during treatment in hypothyroid myopathy. J Clin Pathol 1979;32:229–33.
82. Rumbaugh RC, Kramer RE, Colby HD. Dose-dependent actions of thyroxine on hepatic drug metabolism in male and female rats. Biochem Pharmacol 1978;27:2027–31.
83. Kato R, Takanaka A, Takahashi A. Effect of thyroid hormone on the substrate interaction with p450 in the oxidation of drugs by liver microsomes. J Biochem 1970;68:613–23.
84. Kato R, Takahashi A, Omori Y. Effects of thyroxine and thyroidectomy on the hydroxylation of testosterone by liver microsomes from male and female rats. Biochem Biophys Acta 1970;208:116–24.
85. Eichelbaum M, Bodem G, Gugler R, Schneider-Deters C, Dengler HJ. Influence of thyroid status on plasma half-life of antipyrine in man. N Engl J Med 1974;290:1040–2.
86. Jaffe JH, Martin WR: Opioid analgesics and antagonists. In: Goodman LS, Gilman A, eds. The pharmacological basis of therapeutics. New York: Macmillan 1980:494–534.
87. Halevy S. Effects of anesthesia and surgery on thyroid function. In: Brown BR, Blitt CD, Giesecke AH, eds. Anesthesia and the patient with endocrine disease. Philadelphia: FA Davis, 1980:55–90.
88. Oyama T. Endocrine responses to anaesthetic agents. Br J Anaesth 1973;45:276–81.
89. Oyama T, Shibata S, Matsuki A. Thyroxine distribution during halothane anesthesia in man. Anesth Analg 1969;48:715–9.
90. Oyama T, Shibata S, Matsuki A. Thyroxine distribution during ether and thiopental anesthesia in man. Anesth Analg 1969;48:1–6.
91. Oyama T, Latto P, Haladay DA, Chang H. Effect of isoflurane anaesthesia and surgery on thyroid function in man. Can Anaesth Soc J 1975;22:474–7.
92. Oyama T, Shibata S, Matsuki A, Kudo T. Effect of methoxyflurane anaesthesia on thyroid function in man. Can Anaesth Soc J 1969;16:204–8.
93. Oyama T, Matsuki A, Kodo T. Serum level of thyroxine in man during spinal anaesthesia and surgery. Anaesthesia 1972;27:2–8.
94. Wase AW, Greenspan J. Effect of sodium 5-allyl-5(1-methylbutyl)2-thiobarbiturate on uptake of I^{131} by rat thyroid. Proc Soc Exp Biol Med 1953;84:154–5.
95. Cavalieri RR, Sung LC, Becker CE. Effects of phenobarbital on thyroxine and triiodothyronine kinetics in Graves disease. J Clin Endocrinol Metab 1973;37:308–16.
96. Munson ES, Hoffman JC, DiFazio CA. The effects of acute hypothyroidism and hyperthyroidism on cyclopropane requirement (MAC) in rats. Anesthesiology 1968;29:1094–8.
97. Badad AA, Eger EI II. The effects of hyperthyroidism and hypothyroidism on halothane and oxygen requirements in dogs. Anesthesiology 1968;29:1087–93.
98. Sokoloff L, Wechsler RL, Mangold R, Balls K, Katz SS. Cerebral blood flow and oxygen consumption in hyperthyroidism before and after treatment. J Clin Invest 1953;32:202–8.
99. Smith SE. Sedative and hypnotic drugs and intravenous agents. In: Churchill-Davidson HC, ed. A practice of anaesthesia. Toronto: WB Saunders, 1978:746–84.
100. Pender JW, Fox M, Basso LV. Diseases of the endocrine system. In: Katz J, Benumof J, Kadis LB, eds. Anesthesia and uncommon diseases. Philadelphia: WB Saunders, 1981:155–220.
101. Brown ME, Refetoff S. Transient elevation of serum thyroid hormone concentration after initiation of replacement therapy in myxedema. Ann Intern Med 1980;92:491–5.
102. Carpenter CCJ, Solomon N, Silverberg SG, et al. Schmidt's syndrome (thyroid and adrenal insufficiency): a review of the literature and a report of fifteen new cases including ten instances of co-existent diabetes mellitus. Medicine 1964;43:153–80.
103. Ridgway EC, McCammon JA, Benotti J, Maloof F. Acute metabolic responses in myxedema to large doses of intravenous l-thyroxine. Ann Intern Med 1972;77:549–55.
104. Kudrjavcev T. Neurologic complications of thyroid dysfunction. Adv Neurol 1978;19:619–36.
105. Burrell M, Cronan J, Megna D, Toffler R. Mxyedema megacolon. Gastrointest Radiol 1980;5:181–6.
106. Ritter RN. The effects of hypothyroidism upon the ear, nose and throat: a clinical and experimental study. Laryngoscope 1967;77:1427–79.
107. Graettinger JS, Muenster JJ, Checchia CS, et al. A correlation of clinical and hemodynamic studies in patients with hypothyroidism. J Clin Invest 1958;37:502–10.
108. Sharpey-Schafer EP. Effects of Valsalva's manoeuvre on the normal and failing circulation. Br Med J 1955;1:693–5.
109. Traber DL, Wilson RD, Priano LL. Differentiations of the cardiovascular effects of CI-581. Anesth Analg 1968;47:764–77.
110. Tweed WA, Minuck M, Myrnia D. Circulatory response to ketamine anesthesia. Anesthesiology 1972;37:613–9.
111. Virtue RW, Alanis JM, Mori M, LaFargue RT, Vogel JHK, Metcalf DR. An anesthetic agent: 2-orthochlorophenyl, 2-methylamino cyclohexanone HCl (CI-581). Anesthesiology 1967;28:823–33.
112. Reuler JB. Hypothermia: pathophysiology, clinical settings and management. Ann Intern Med 1978;89:519–27.
113. Forester CF. Coma in myxedema. Arch Intern Med 1963;111:734–43.

CLINICAL reports

Pericardial Effusion and Severe Tachycardia

G. J. Moon, MD*

In patients with pericardial effusion or tamponade, cardiac output (CO) decreases because of decreases in preload (1, 2) (inhibition of diastolic expansion) and stroke volume (SV). At the same time, however, enhanced sympathetic tone (3) produces a compensatory tachycardia. A heart rate of 140 to 160 beats per minute is frequently seen in these patients, and bradycardia should be avoided.

We recently treated a patient with pericardial effusion who experienced sudden, severe tachycardia (QRS rate 180 to 210 beats per minute) accompanied by circulatory collapse shortly after anesthesia had been induced.

Case Report

A 62-year-old, well-built, black man with pericardial effusion of unknown origin was scheduled for a pericardial window procedure. A large cardiac silhouette had appeared on a routine chest roentgenogram 1 year earlier. The patient had no history of diabetes mellitus, renal disease, cancer, tuberculosis or other infectious disease, angina, myocardial infarction, hypertension, or arrhythmia. Three months earlier pericardiocentesis had been performed at another hospital, but the patient refused the pericardial window procedure at that time because he was relatively asymptomatic. Before admission to our hospital, he felt shortness of breath and chest congestion after heavy physical work. Pericardiocentesis done the day before the present procedure was unsuccessful, and only 20 ml of amber-colored fluid was obtained.

Although it was estimated from an echocardiogram that approximately 2 L of pericardial fluid was present, the patient felt no discomfort and his neck veins were not noticeably distended. Pulsus paradoxus recorded earlier was 14 to 16 mm Hg. The only premedication was atropine, 0.4 mg, given intramuscularly 1 hour before induction of anesthesia. Because the patient's symptoms and signs were mild, central venus and radial arterial cannulations were not done.

Immediately before induction of anesthesia the electrocardiogram showed sinus tachycardia with a rate of 140 beats per minute. Blood pressure was 110/70 mm Hg. Anesthesia was induced with diazepam (5 mg), ketamine (100 mg), and thiopental (150 mg) with succinylcholine (80 mg) being given for tracheal intubation. After intubation, heart rate and blood pressure remained approximately the same. Nitrous oxide was started and pancuronium (3 mg) was given.

Approximately 10 minutes after intubation (approximately 15 minutes after induction started), his heart rate suddenly increased from 140 to 180 beats per minute and his blood pressure decreased. Korotkoff sounds by blood pressure cuff at first were faintly heard at 50 torr, but then could not be heard. Soon the radial pulse was not palpable. The heart rate (by ECG) increased further to 210 beats per minute. Whether this cardiac rhythm was paroxysmal arterial tachycardia, a trial fibrillation, atrial flutter with AV block, or fast junctional rhythm could not be determined at this time. The rate of intravenous infusion of fluids was increased so that approximately 400 ml of 5% deoxtrose in water was given over the next 10 minutes. The carotid sinus was massaged, and methoxamine was given intravenously three times (total: 8 mg) without effect on the heart rate. Within several minutes, with a DC fibrillator at hand, the patient's chest was opened on the left side. However, by this time, the heart rate had decreased to 120 beats per minute and systolic blood pressure increased to 100 mm Hg. Thereafter, the patient's vital signs remained stable.

Approximately 700 ml of brownish fluid was removed from the pericardial sac, and the pericardial window procedure was performed uneventfully. Pyridostigmine (10 mg) and glycopyrrolate (0.4 mg) were given intravenously at the end of the procedure.

In the recovery room, the patient was awake and breathing well. His heart rate (sinus tachycardia) ranged from 120 to 136 beats per minute. However, in the coronary care unit,

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Received from the Department of Anesthesiology, Henry Ford Hospital, 2799 West Grand Boulevard, Detroit, Michigan 48202. Accepted for publication December 10, 1981.

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the patient again experienced severe tachycardia and was found to have atrial flutter with 2:1 AV bock. Digoxin and later proporanolol were given to control the heart rate.

The pathologist's report found no fungal organisms or acid-fast bacilli on special stains, but the thickened pericardium contained scattered, noncaseating tuberculoid granulomata.

Discussion

Pericardial effusion or tamponade may be caused by infection (viral, bacterial, fungal), chest trauma (penetrating, blunt), malignancy (4) (usually metastatic), myocardial infarction (5), or uremia (6). Iatrogenic causes include complications associated with central venous catheterization (7) or placement of an intravenous pacemaker wire.

As the fluid (exudate, blood, or mixture) accumulates in the pericardial cavity, diastolic expansion of the heart chambers is inhibited. Stroke volume and cardiac output decrease but are compensated for by enhanced sympathetic tone and tachycardia. Arterial blood pressure is relatively well maintained due to peripheral constriction. However, beyond a certain point, as pericardial fluid continues to accumulate, blood pressure decreases precipitously. Nerlich (8) classified this uncompensated stage as phase II.

Although removal of the pericardial fluid by pericardiocentesis, or through a subxyphoidal opening (9) using local anesthetics, restores cardiac function these procedures cannot always be done promptly or effectively. Moreover, there have been numerous reports of arrest during the procedures themselves, especially when cardiac tamponade is severe or develops rapidly.

An important aspect of our case is the relationship between the autonomic nervous system and heart rate. Although enhanced sympathetic activity increases heart rate, vagal tone may also increase, which tends to slow the heart rate (10, 11). In many cases of cardiac tamponade, it has been reported that tachycardia suddenly becomes replaced by bradycardia just before circulatory arrest. In induced cardiac tamponade in dogs, Friedman et al (12) described this sudden bradycardia as a vagal depressor reflex. Sudden bradycardia is also seen in any cardiac arrest from other causes. It is tempting to interpret this phenomenon as a delicately balanced system in which the two branches of the autonomic nervous system, regulated by the hypothalamus, check each other and prevent either from running out of control.

Even though our patient had chronic accumulation of only moderate amounts of effusion, it was thought that he might be vulnerable to vagal bradycardia, and atropine was available to be given at any time. Instead, the patient developed severe tachycardia followed by cardiovascular collapse. To my knowledge circulatory arrest associated with tachycardia of this degree in patients with pericardial effusion has not been reported in the literature. It is not clear why this patient, who had no history of arrhythmia, developed such severe tachycardia. Pancuronium and/or ketamine may have been possible contributing causes in the development of this tachycardia, but two points suggest this is unlikely. First, these drugs were given intravenously approximately 10 minutes before the development of the severe tachycardia. If these drugs were the cause, the tachycardia should had appeared earlier than 10 minutes. Second, a similar episode recurred in the coronary care unit hours after these drugs had been given.

Another noteworthy feature of this case is the relationship of heart rate to cardiac output and arterial blood pressure. If the heart rate is increased by means of a pacemaker, cardiac output gradually increases. However, beyond the peaks of approximately 130 beats per minute, cardiac output starts to decline (13) because the occurrence of tachycardia at a rate greater than 130 beats per minute does not provide enough time for effective filling of the heart chambers. In contrast, when tachycardia is induced by enhanced sympathetic activity, maximum cardiac output is obtained at approximately 180 beats per minute (13) in the young adult. The reason is that increased, rapid contraction and relaxation of the heart chambers caused by sympathetic activity provides more time for effective filling, along with systemic vasoconstriction. Change in blood pressure is likely to take the same course as that of cardiac output.

In normal hearts without pericardial effusion, a heart rate of 180 beats per minute with enhanced sympathetic activity will not cause hypotension less than 50 torr, and it can be assumed that the sympathetic activity in our patient increased at least moderately. It can also be assumed that left ventricular function in this patient with chronic effusion of 700 ml was approximately normal. Indeed, a cardiac catheterization done 3 months earlier showed normal left ventricular function. The preload limit already present as a result of the pericardial effusion, in addition to heart rate of 180 beats per minute, might have contributed to his severe hypotension. Therefore, our primary aim in treating this patient was to lower his heart rate.

In summary, a case of circulatory collapse due to

severe tachycardia in a patient with pericardial effusion was presented. Control of reasonable heart rates seems to be the main therapeutic measure in such a case.

ACKNOWLEDGMENTS

The author thanks Patricia L. Cornett, PhD for editing the manuscript, and Cherrye Schrecklinger for secretarial assistance.

REFERENCES

1. Isaacs FP, Berglund E, Sarnoff SJ. Ventricular function. III. The pathology physiology of acute cardiac tamponade studied by means of ventricular function curve. Am Heart J 1954;48:66.
2. Frank MJ, Nadimi M, Lesniak LJ. Effects of cardiac tamponade on myocardial performance, blood flow, and metabolism. Am J Physiol 1971;220:179–85.
3. Nakano J, DeSchryrer CD. Effects of acute cardiac tamponade on circulatory dynamics and catecholamine plasma levels. Cardiologia 1963;43:86–93.
4. Pories WJ, Gaudiani VA. Cardiac tamponade. Surg Clin North Am 1975;55:573–89.
5. Kendall RW, DeWood MA. Postinfarction cardiac rupture: surgical success and review of the literature. Ann Thorac Surg 1978;25:311–5.
6. Morin JE, Hollomby D, Gonda A, Long R, Dobell ARC. Management of uremic pericarditis: a report of 11 patients with cardiac tamponade and a review of the literature. Ann Thorac Surg 1976;22:588–92.
7. Defalque RJ, Campbell C. Cardiac tamponade from central venous catheters. Anesthesiology 1979;50:249–52.
8. Nerlich WE. Determinants of impairment of cardiac filling during progressive pericardial effusion. Circulation 1951;3:377–83.
9. Fontenelle LJ, Cuello L, Dooley BN. Subxiphoid pericardial window. J Thorac Cardiovasc Surg 1971;62:95–7.
10. Guyton AC, Jones CE, Coleman TG. Circulatory physiology: cardiac output and its regulation. 2nd ed. Philadelphia: WB Saunders, 1973:306–8.
11. Levy MN. Parasympathetic control of the heart. In: Randall WC, ed. Neural regulation of the heart. Philadelphia: WB Saunders, 1977:98.
12. Friedman HS, Lajam F, Gomes JA, Zaman Q, Marino ND, Calderon J. Demonstration of a depressor reflex in acute cardiac tamponade. J Thorac Cardiovasc Surg 1977;73:279–86.
13. Smith JJ, Kampine JP. Circulatory physiology—the essentials. Baltimore: Williams & Wilkins, 1980:121.

Effect of Inspiratory Flow Rate on Gas Exchange during Mechanical Ventilation

The effect of changes in inspiratory flow rate ($\dot{V}_I$) on gas exchange and respiratory system mechanics was studied during mechanical ventilation. Seven patients with respiratory failure caused by severe chronic airway obstruction (CAO group) and six patients with other causes of respiratory failure (ORF group) were studied at three $\dot{V}_I$ settings, 40 L/min, 70 L/min, and 100 L/min. In the CAO group, as $\dot{V}_I$ increased from 40 L/min to 100 L/min, arterial oxygen tension increased 18%, venous admixture decreased 23.2%, dead space to tidal volume ratio decreased 23.7%, and tidal compliance of the respiratory system increased 31.2%. In the ORF group, as $\dot{V}_I$ increased, there was little change in most parameters measured. The changes in the CAO group may be explained by redistribution of ventilation to low ventilation-perfusion ratio units, which empty more completely during the longer expiratory times allowed at high $\dot{V}_I$. A simple two-compartment lung model demonstrated that an increase in expiratory time from 4.2 to 6.1 seconds (the increase observed in the CAO group as $\dot{V}_I$ increased from 40 L/min to 100 L/min) will result in redistribution of ventilation to long expiratory time constant respiratory units and produce changes in lung mechanics and gas exchange similar to those observed experimentally. The authors conclude that mechanical ventilation at high $\dot{V}_I$ in patients with CAO is associated with improvement in gas exchange and more even distribution of ventilation, which appear to be due to the increased time available for alveolar emptying. *(Connors AF Jr, McCaffree DR, Gray BA. Effect of inspiratory flow rate on gas exchange during mechanical ventilation. Am Rev Respir Dis 1981;124:537–43)*

ANESTH ANALG
1982;61:387-9

Hypotension following Contrast Media Injection during General Anesthesia

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The intravenous injection of contrast media in the conscious patient is occasionally associated with minor or severe reactions. Such reactions have not been reported in anesthetized patients.

This report concerns two patients who showed severe hypotensive responses during arteriography under general anesthesia.

Case Reports

Case 1

A 6-year-old boy had been diagnosed as having a nephroblastoma at age 3½ years, and had been treated with right nephrectomy, chemotherapy, and radiation. There had been subsequent admissions and procedures including a left nephrectomy, a shunt procedure from the left posterior tibial artery to the greater saphenous vein, and a left cephalic vein to radial artery fistula. Dialysis was carried out regularly and there were two additional anesthetic procedures for revision of the fistula. The child had no known allergies or problems with previous anesthetics.

For the present procedure, he was premedicated with chloral hydrate, 800 mg, orally. Weight was 20 kg, arterial pressure 180/100 mm Hg, heart rate 110 beats per minute, and temperature 38.2°C; serum electrolyte levels and chest roentgenograms were normal. General anesthesia for the proposed revision of the saphenous to posterior tibial shunt included thiopental, 50 mg, and succinylcholine, 10 mg, intravenously, with maintenance on endotracheal nitrous oxide, oxygen, and halothane (1.5%). Ventilation was assisted throughout; the anesthetic course was initially uneventful. Following thrombectomy, the surgeon planned a shunt angiogram. Arterial pressure was 120/50 mm Hg, and heart rate 110 beats per minute. Diatrizoate meglumine (Renovist), 10 ml, was injected into the saphenous vein, followed 4 minutes later by 10 ml into the tibial artery. Three minutes after the second injection, the patient began to hyperventilate, with a respiratory rate of 30 breaths per minute; there was sinus tachycardia of 150 beats per minute and arterial pressure decreased to 60 mm Hg systolic. The anesthetics were discontinued and 100% oxygen was given. Intravenous fluids were infused rapidly. The tachycardia and hypotension persisted, and during the next 15 minutes a total of 250 ml of dextrose in saline was given intravenously, together with hydrocortisone sodium succinate, 100 mg; diphenhydramine (Benadryl), 25 mg; and phenylephrine to a total dose of 550 μg. The arterial pressure then stabilized at approximately 100/50 mm Hg and the heart rate at 110 beats per minute. The patient was taken to the recovery room and the postoperative course was uneventful.

Case 2

A 55-year-old woman had severe peripheral vascular artherosclerotic disease. Her clinical history included removal of a parathyroid adenoma, left pyelolithotomy, left nephrectomy and splenectomy, aortobifemoral bypass, and bilateral lumbar sympathectomy. There was no history of diabetes mellitus, myocardial infarction, or allergy.

On this admission, translumbar and bilateral femoral arteriograms were planned under general anesthesia. Before surgery, laboratory data and chest roentgenogram were normal. The electrocardiogram showed an incomplete right bundle branch block, arterial pressure was 150/90 mm Hg, and heart rate 70 beats per minute. Premedication included meperidine, 50 mg; hydroxyzine, 25 mg; and atropine, 0.4 mg, intramuscularly.

General anesthesia was induced with thiopental and succinylcholine and maintained endotracheally with nitrous oxide, oxygen, and 0.5% halothane; pancuronium and fentanyl were also given. Cuff arterial blood pressure, electrocardiogram, urine output and temperature were monitored.

A thrombus was demonstrated in the right limb of the aortobifemoral graft, and a thrombectomy and revision of the graft were performed with the patient's condition remaining stable throughout. An arteriogram was then obtained using 20 to 30 ml of Renovist injected into the femoral portion of the graft. Three minutes later, the arterial pressure could not be obtained and heart rate had increased from 60 to 120 beats per minute. Approximately 700 ml of Ringer's lactate was injected intravenously over the next 5 minutes, together with 200 mg of hydrocortisone, 20 mg of ephedrine, and phenylephrine to a total of 400 μg. Arterial pressure increased to 110/80 mm Hg after 15 minutes; heart rate was 100 beats per minute. At the end of the procedure, her cardiovascular status was stable and the patient awoke quickly and was extubated. Recovery was uneventful.

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Received from the Division of Anesthesiology and Department of Radiology, Cleveland Clinic Foundation, Cleveland, Ohio. Accepted for publication December 17, 1981.
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Discussion

The two patients in this report developed severe hypotension and tachycardia, apparently as an acute reaction to the intra-arterial injection of modest doses of contrast medium. There was no change in the conduct of anesthesia or evidence of surgical bleeding to explain the events. Approximately 10 minutes were required before the blood pressure responded to high doses of vasopressors, steroids, antihistamines, and fluids. Each patient had had injections of contrast media in the past, in both the conscious and anesthetized states, without adverse response.

Reactions to contrast media in awake patients have been well documented, notably by Ansell (1), who recorded the incidence of adverse responses to uroangiographic solutions as follows: fatal, 1 in 40,000; "severe," 1 in 20,000; and "mild," 1 in 2,000 administrations. Explanations for these reactions ranged from antigen-antibody interaction, complement activation, and histamine release, to an effect of the contrast medium on the central nervous system, especially in overanxious patients.

In the incidents described here, the injections were made at some distance from the heart and lungs and would have arrived there in diluted strength. It is difficult, therefore, to attribute a specific etiology, such as either histamine release from pulmonary mast cells or cardiac slowing from a direct effect on the sinus node and on atrial ventricular conductivity caused by the ionic composition of contrast solutions (2). The same doubt seems to apply to a possible reduction in calcium ions, and an altered extracellular sodium/potassium ratio, leading to myocardial depression (2, 3). It is also questionable that the tachycardia and hypotension could be specifically attributed to either vagal inhibition or sympathetic stimulation. The previous experience with these patients and the nature of the response occurring under general anesthesia does not suggest that the reaction observed in our cases was due to an antigen-antibody reaction or other immunologic response.

Another hypothesis, suggested by Lasser et al (4), is that contrast media may cause temporary absence of sufficient C-1 esterase inhibitor, thus allowing activation of kinins and the complement system. This reaction would more likely result in thrombosis, rather than the acute hypotension and tachycardia experienced in our patients.

Contrast media, in their present ionic form, and in large volumes, are capable of causing tissue damage, especially when injected into the cerebral, cardiac, or renal circulations. Blood elements, endothelial cells, and other local tissues can be destroyed. Resultant poor tissue oxygenation associated with injection of contrast media may be serious enough even in the absence of severe hypotension noted in our cases.

Hypotension and tachycardia in the conscious patient may be associated not only with blood loss, but also with manipulations such as introduction of catheters by the Seldinger technique, in the absence of contrast media. These responses can best be explained on the basis of an autonomic reflex with peripheral vasodilation which leads to hypotension and reflex tachycardia.

It is generally considered unusual for reactions to contrast media to occur in anesthetized patients. However, Malins (5) has reported pulmonary edema in five patients during femoral arteriography; in these patients, however, the volume of contrast medium was significantly greater than the mean volumes injected in another 63 individuals who did not show adverse reactions. In the laboratory, toxic or near-toxic doses have produced adverse responses, including death, during anesthesia. However, the LD_{50} of contrast media injected in experimental animals is considerably higher in the anesthetized state (6, 7).

Hoppe and Archer (8) and Lalli and Greenstreet (9, 10) have suggested that adverse responses to contrast media result from an action on the central nervous system, particularly the autonomic divisions. The question arises, therefore, whether these types of reactions may occur in anesthetized patients. The combination of tachycardia with hypotension evoked by contrast media in the two patients described here suggests that the level of anesthesia did not prevent reactions which seem to have been directly or indirectly mediated by the autonomic nervous system.

In summary, two patients developed profound hypotension and tachycardia following the intra-arterial injection of small doses of contrast medium, while anesthetized for surgical procedures. They had both received similar injections on previous occasions, while awake or anesthetized, without complications. The responses were difficult to reverse and have not been described previously in anesthetized patients. Although the pathophysiologic mechanisms remain obscure, several possibilities have been considered.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the help and advice of R. A. Millar, MD and A. R. Boutros, MD in preparing this manuscript.

REFERENCES

1. Ansell G. Adverse reactions to contrast agents. Scope of problem. Invest Radiol 1970;5:374–84.

2. Higgins CB. Effects of contrast media on the conducting system of the heart. Radiology 1977;124, 3:599–606.
3. Zipfel J, Baller D, Blanke H, et al. Decrease in cardiotoxicity of contrast media in coronary angiography by addition of calcium ions: a combination experimental and clinical study. Clin Cardiol 1980;3:178–83.
4. Lasser EC, Slivka J, Lang JH, et al. Complement and coagulation: considerations in contrast catastrophies. Am J Roentgnol 1979;132:171–6.
5. Malins AF. Pulmonary edema after radiological investigation of peripheral occlusive vascular disease: adverse reaction to contrast media. Lancet 1978;1:413–5.
6. Lasser EC, Elizonda-Martel G, Granke RC. The roentgen contrast media potentiation of Nembutal anesthesia in rats. AJR 1964;91:453–60.
7. Ziperman HH, Hughes RR, Shumacker HB. The effect of barbiturates and other drugs on mortality from Diaderast in the mouse. Angiology 1950;1:427–31.
8. Hoppe Jo, Archer S. X-ray contrast media for cardiovascular angiography Angiology 1960;11:244–54.
9. Lalli AF. Contrast media reactions: data analysis and hypothesis. Radiology 1980;134:1–12.
10. Lalli AF, Greenstreet R. Reactions to contrast media: testing the CNS hypothesis. Radiology 1981;13:47–9.

Intravenous Nitroglycerin during Surgery for Coronary Artery Disease

The effects of a continuous infusion of nitroglycerin in the period preceding cardiopulmonary bypass were studied in patients undergoing elective coronary artery surgery. All patients had received long-term beta blockade therapy. Anesthesia consisted of nitrous oxide (50%), pancuronium, and fentanyl (approximately 15 μg/kg during study period). Twenty-eight patients were randomly assigned to either a control group (14 patients) or a nitroglycerin group (14 patients), in which intravenous nitroglycerin was administered after induction. The initial infusion rate was 0.5 μg/kg/min. Immediately before the skin incision, the infusion rate was increased to 3 μg/kg/min. Nitroglycerin decreased systemic systolic, pulmonary systolic, and wedge pressures without changing heart rate, diastolic pressure, or cardiac index, thus leading to an improvement in endocardial viability ratio. The use of a nitroglycerin bolus to abort an acute myocardial ischemic episode is described. *(Kaye SE, Dimai W, Gattiker R. Intravenous nitroglycerin during surgery for coronary artery disease. Anaesth Intensive Care 1981;9:247–54)*

Airway Response to Sublingual Nitroglycerin in Acute Asthma

To test the efficacy of sublingual nitroglycerin as a bronchodilator, 10 patients with acute asthma were studied. After a base line spirogram, each patient was given 1.2 mg of sublingual nitroglycerin, and subsequent spirograms were obtained at 5-minute intervals for 15 minutes. Each patient was then given three subsequent doses of epinephrine (0.5 mg) subcutaneously at 15-minute intervals. Spirograms were obtained 15 minutes after each epinephrine dose. Forced expiratory volume at 1 second (FEV_1) and forced vital capacity (FVC) did not change significantly following sublingual nitroglycerin, but both FEV_1 and FVC improved significantly after epinephrine administration. Three patients experienced transient but severe hypotension after receiving sublingual nitroglycerin. The results suggest that sublingual nitroglycerin is not adequate initial therapy for asthmatic attacks and that the administration of sublingual nitroglycerin may be dangerous for patients with acute asthma. *(Kennedy T, Summer WR, Sylvester J, Robertson D: Airway response to sublingual nitroglycerin in acute asthma. JAMA 1981;246:145–7)*

ANESTH ANALG
1982;61:390-2

Cerebral Infarction following Spinal Anesthesia for Cesarean Section

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Cerebral infarction secondary to cerebral venous thrombosis rarely complicates pregnancy and the puerperium, and to our knowledge this problem has not been reported following spinal anesthesia. This case describes cerebral venous thrombosis following spinal anesthesia and the early signs and symptoms that may be similar to postlumbar puncture headache.

Case Report

Following an uneventful term pregnancy a healthy 29-year-old primigravida was scheduled for an electrive cesarean section because of breech presentation. Lumbar epidural anesthesia was requested; however, attempts to introduce a catheter into the epidural space at both L2-3 and L3-4 through an 18-gauge Hustead needle resulted in intravascular catheter placement. Consequently, epidural anesthesia was abandoned in favor of spinal anesthesia. The subarachnoid space was entered on the first midline attempt at L3-4 with a 25-gauge spinal needle. A mixture of 8 mg of 1% tetracaine and 1.0 ml of 10% dextrose in water injected into the subarachnoid space produced a bilateral sensory level at T-5. The patient's preanesthetic blood pressure of 110/65 torr never decreased to less than 105/55 torr subsequent to a preloading intravenous volume of 2000 ml of lactated Ringer's solution and left uterine displacement. An uneventful cesarean section resulted in the delivery of a vigorous infant.

On the second postoperative morning the patient complained of throbbing nuchal pain associated with the upright position. If she remained upright, a throbbing frontal headache would ultimately develop. These symptoms remitted rapidly with assumption of the supine position. The diagnosis of postlumbar puncture headache was made and the possibility of an epidural blood patch was discussed with the patient. She declined and followed a regimen of vigorous hydration and bed rest. On the fourth postoperative day the patient requested a blood patch because of continuing headache. A fever of 38°C had been present earlier in the day, and we decided to postpone the blood patch until she had been afebrile for 24 hours. As the patient desired to be discharged that day, she was instructed to take her temperature at home and to return for an epidural blood patch when she remained afebrile for 24 hours if her headache persisted.

The patient was readmitted to the hospital the following afternoon immediately following two grand mal seizures. On admission, although lethargic, she was conscious and fully oriented. Blood pressure was 110/70 torr, pulse 112 beats per minute, and respiratory rate 20 breaths per minute. Her pupils were equal and reactive to light, and accommodation and the fundi were normal. There were no signs of meningeal irritation or carotid bruits. Further neurologic examination revealed athetoid movements of the right arm which rapidly disappeared spontaneously and slight weakness in the left arm and left leg. Weakness of the leg exceeded that of the arm. Cranial nerves II to XII were intact. Deep tendon reflexes were equal and there was no clonus. The chest was clear and the cardiac examination was normal. Blood chemistry data on admission were normal with the following exceptions: inorganic phosphorus, 1.9 mg/dl; alkaline phosphatase, 153 units/L; lactic dehydrogenase 387 units/L; and slightly elevated levels of cholesterol and triglycerides. The hematocrit was 41.9%, hemoglobin 14.6 g/dl, and white blood cell 14.4 × 10^3/mm^3 with 69% polymorphonuclear and 17% band cells. Prothrombin time, partial thromboplastin time, and platelet count were within the normal range.

Computed tomography (CT) of the brain was consistent with a small hemorrhagic infarction or intracerebral hemorrhage high on the convexity of the right frontal area. A technetium-99m brain scan on the second hospital day was interpreted as normal for both static and flow studies. The electrocardiogram and chest roentgenogram were normal whereas an echocardiogram showed probable late systolic mitral valve prolapse.

The neurologist diagnosed a small cortical venous thrombosis as the cause of the hemorrhagic cerebral infarction. The patient remained afebrile following admission and her left hemiparesis almost completely resolved after 4 days. She was discharged on the fourth hospital day and remains well, her only neurologic sequela being a focal motor seizure disorder involving the left leg.

Discussion

Several observers (1-5) have reported cerebral infarction in pregnancy (primarily third trimester) and

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Received from the Department of Anesthesia, Bowman Gray School of Medicine of Wake Forest University, Winston-Salem, North Carolina. Accepted for publication December 24, 1981.
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the puerperium resulting from venous or occasionally arterial occlusion. In Western countries this complication arises in approximately 1/1,666 to 1/10,000 obstetric admissions, whereas in India the rate is 1/225 (1). In our experience this is the first case in 16,000 obstetric admissions. Venous and venous sinus lesions occur more frequently than arterial lesions, and the smaller venous lesions, as exemplified by our patient, usually carry a good prognosis with near complete recovery. The high mortality rate seen in cerebral venous thrombosis (27% to 45%) is primarily accounted for by cases of sagittal sinus thrombosis.

The etiology of cerebral venous thrombosis in this setting is probably a combination of the hypercoagulable state of pregnancy and the puerperium and an anatomic susceptibility for thrombogenesis in the cortical venous system. The hypercoagulability results from an increase in coagulation factors VII (6), VIII (7), and X (6), hyperfibrinogenemia (8), increased platelet number and adhesiveness (9, 10), and either a relative (8) or absolute (11, 12) decrease in fibrinolysis. The anatomic and hemodynamic factors that increase thrombogenicity in cerebral cortical veins include low intravascular pressures, absence of valves, transient alteration in flow with coughing and sneezing, and the acute angle formed by their junction with the sagittal sinus (13).

In the absence of definitive angiography, the diagnosis of cerebral venous thrombosis is, as in this case, made on clinical grounds. The premonitory symptoms of headache and low grade fever may precede by days the onset of seizures, neurologic deficit, and altered consciousness. Our patient exhibited all of these symptoms with the exception of altered consciousness. The hemorrhagic infarction which frequently occurs was demonstrated on CT scan. Her headache, however, rather than being unilateral, persistent, and limited to the forehead, temple, or occiput, as is characteristic of cerebral venous thrombophlebitis (1), was bilateral and posturally related. It was therefore clinically diagnosed as postlumbar puncture headache secondary to a cerebrospinal fluid leak. Cerebral vein thrombosis was not initially suspected. In retrospect, we believe that the patient probably concurrently had a spinal fluid leak and early cerebral thrombophlebitis.

Numerous intracranial lesions may be causally related to lumbar puncture or spinal anesthesia and initially produce headache symptoms. Cranial nerve III to VIII paralysis has been reported (14) as have acute subdural hematoma (15, 16) and herniation of the cerebral uncus (17). Schube and Raskin (18) cited numerous cases of acute intracerebral bleeding following diagnostic lumbar puncture, but all in patients with existing mass lesions. In all these cases the etiology of the lesion is probably a small cerebral shift secondary to cerebrospinal fluid loss.

Even if our patient's headache was primarily the result of a cerebrospinal fluid leak rather than phlebothrombosis, we cannot postulate a physiologic mechanism whereby such cranial decompression could cause cerebral vein thrombosis. Furthermore, as cerebrovascular autoregulation prevents spinal anesthesia from significantly affecting cerebral blood flow, except with extreme hypotension (19–21), blood stasis cannot be implicated as a causative factor.

Therefore, we believe that the lumbar puncture and cerebral vein thrombosis occurred coincidentally and were causally unrelated. In view of the widespread use of spinal anesthesia and the frequency of inadvertent lumbar puncture with epidural anesthesia in pregnancy, this case emphasizes that headache following lumbar puncture in the pregnant or puerperal patient occasionally may signify grave problems such as cerebral vein thrombosis. Headaches following lumbar puncture should be thoroughly investigated and not assumed a priori to represent simply the headache of cerebrospinal fluid leak.

REFERENCES

1. Bansal BC, Gupta RR, Prakash C. Stroke during pregnancy and puerperium below the age of 40 years as a result of cerebral venous/venous sinus thrombosis. Jpn Heart J 1980;21:171–83.
2. Amias AG. Cerebral vascular disease in pregnancy. II. Occlusion. J Obstet Gynaecol Br Commonw 1970;77:312–25.
3. Gupta OP, Tewari IJ, Mital VN. Primary cerebral thrombophlebitis of puerperium. J Indian Med Assoc 1977;68:160–3.
4. Lavin PJM, Bone I, Lamb JT, Swinburne LM. Intracranial venous thrombosis in the first trimester of pregnancy. J Neurol Neurosurg Psychiatry 1978;41:726–9.
5. Estanol B, Rodriguez A, Conte G, Aleman JM, Loyo M, Pizzuto J. Intracranial venous thrombosis in young women. Stroke 1979;10:680–4.
6. Pechet L, Alexander B. Increased clotting factors in pregnancy. N Engl J Med 1961;265:1093–7.
7. Todd ME, Thompson JH Jr, Bowie EJW, Owen CA Jr. Changes in blood coagulation during pregnancy. Mayo Clin Proc 1965;40:370–83.
8. Fletcher AP, Alkjaersig NK, Burstein R. The influence of pregnancy upon blood coagulation and plasma fibrinolytic enzyme function. Am J Obstet Gynecol 1979;134:743–51.
9. Wright HP. Changes in the adhesiveness of blood platelets following parturition and surgical operations. J Pathol Bacteriol 1942;54:461–8.
10. Prakash C, Arya RK, Singla KP, Bansal BC. Study of platelet adhesiveness and serum lipids in cerebral venous/venous sinus thrombosis during puerperium. J Assoc Physicians India 1970;18:815–9.
11. Bansal BC, Prakash C, Gupta RR, Brahmanandam KRV. Study

of serum lipid and blood fibrinolytic activity in cases of cerebral venous/venous sinus thrombosis during the puerperium. Am J Obstet Gyecol 1974;119:1079–82.
12. Gillman T, Naidoo SS, Hathorn M. Plasma fibrinogen activity in pregnancy. Lancet 1959;2:70–1.
13. Merwarth HR. Hemiplegia of corticol or venous origin. Brooklyn Hosp J 1940;2:193–212.
14. Lee JJ, Roberts RB. Paresis of the fifth cranial nerve following spinal anesthesia. Anesthiology 1978;49:217–8.
15. Pavlin DJ, McDonald JS, Child B, Rusch V. Acute subdural hematoma—an unusual sequela to lumbar puncture. Anesthesiology 1979;51:338–40.
16. Edelman JD, Wingard DW. Subdural hematomas after lumbar dural puncture. Anesthesiology 1980;52:166–7.
17. Eerola M, Kaukinen L, Kaukinen S. Fatal brain lesion following spinal anaesthesia. Acta Anaesthesiol Scand 1981;25:115–6.
18. Schube PG, Raskin N. Cerebral hemorrhage following lumbar puncture. J Nerv Ment Dis 1936;84:636–59.
19. Greene N. Physiology of spinal anesthesia. 3rd ed. Baltimore: Williams & Wilkins, 1981.
20. Hampton LJ, Little DM, Jr. Complications associated with the use of "controlled hypotension" in anesthesia. Arch Surg 1953;67:549–56.
21. Gillies J. Hypotension in anesthesia. Br Med J 1953;1:504–5.

Myocardial Salvage after Intracoronary Thrombolysis with Streptokinase

Nine patients with acute myocardial infarction had cardiac catheterization and intracoronary infusions of streptokinase 2.3 to 4.3 hours (mean 3.5) after the onset of symptoms. Occluded coronary arteries were opened within approximately 20 minutes in all patients, but reocclusion occurred in one patient. The immediate effect of thrombolysis on myocardial salvage was assessed with the intracoronary injection of thallium-201. Improved regional perfusion, indicating myocardial salvage after recanalization, was observed in seven of the nine patients. One patient, who had also sustained a nontransmural infarction the previous week, had no change after thrombolysis. In the ninth patient, recanalization of a coronary artery was followed by reocclusion and worsening of the myocardial perfusion defect. Intracoronary thallium-201 studies two weeks and three months after streptokinase infusion in two patients were unchanged in comparison with scintiscans performed 1.5 hours after thrombolysis. These short-term observations suggest that recanalization of obstructed coronary arteries after intracoronary thrombolysis can salvage jeopardized myocardium. However, evaluation of the long-term effects of this procedure on survival and myocardial function will require controlled clinical trials. *(Markis JE, Malagold M, Parker JA, et al: Myocardial salvage after intracoronary thrombolysis with streptokinase in acute myocardial infarction: assessment by intracoronary thallium-201. N Engl J Med 1981;305:777–82)*

letters
TO THE EDITOR

Paradoxical Inhibition of Decreases in Body Temperature by Use of Heated and Humidified Gases

To the Editor:

Recently Stone et al (1) studied the effects of heating and humidification of respiratory gases on core temperatures of patients during anesthesia and surgery. We would like to add to their discussion.

The amount of heat transferred to or from the body can be calculated by the modified formula for the mean total body temperature (2):

$$\Delta BH = \{0.66(T_c^2 - T_c^1) + 0.34(T_s^2 - T_s^1)\}\ 0.83 \times BW$$

where T_c and T_s represent the core and skin temperatures (°C), respectively, ΔBH the change in total body heat content (kcal), 0.83 the specific heat of the body (kcal/kg/°C) and BW the body weight (kg). Application of this formula to the patients of Stone et al (1) during the 1st hour of anesthesia (group 1) indicates a negative heat balance of approximately 75 kcal. The treated group (group II) has a balance of 0 kcal. This suggests that humidification and heating of respiratory gases prevents a heat loss of 75 kcal, or supplies 75 kcal, or a combination of both. However, if we calculate the amount of heat involved, we find that their measures could at the most prevent 10 kcal/hr from leaving the body or being supplied to the body via the airways. Thus, this small amount cannot begin to explain the normal temperatures in the patients of Stone et al (1) in group II.

To calculate the heat transfer by gases and the heat loss or gain due to water evaporation or condensation we can use the following formula:

$$\Delta HT + \Delta H_{H_2O} = \dot{V} \cdot \{0.3(T_g^2 - T_g^1) + 0.585\ (C_g^2 - C_g^1)\}$$

where ΔHT is heat transfer by the gas itself (kcal/hr), ΔH_{H_2O} is heat transfer due to evaporation or condensation (latent heat) of the water in the gases (kcal/hr), $\dot{V}$ is the respiratory gas exchange (m^3/hr), T_g the gas temperature (°C), 0.585 is the evaporation or condensation heat of water (kcal/ml), and C_g is the amount of water in the gas (ml/m^3). The gas in a semiclosed circle system is approximately 25°C and has a 40% relative humidity. The amount of water varies between 20 and 45 ml/m^3 if the gas temperatures vary from 20 to 38°C. From this formula we know that the patients of Stone et al (1) lost approximately 4.5 to 8 (kcal/hr) through the airways (group 1) and that group II was supplied up to 2 kcal/hr through the airways. Thus the heat balance could be affected no more than 10 kcal in the 1st hour of anesthesia, which is much less than the 75 kcal theoretically needed for the maintenance of normal temperature in their patients. A similar discrepancy is found in the studies reported by Chalon et al (3). Both authors used nasopharyngeal temperature measurements and do not discuss their paradoxical findings.

A possible explanation for the discrepancies between the measured and the expected temperatures in the patients studied by Stone et al (1) could be that heating and humidification of respiratory gases affect metabolism and conservation mechanisms for body heat indirectly, in addition to the direct heat transfer effects. A more likely explanation is that heating and humidifying gases warm the nasopharynx causing erroneous "core temperature" measurements. This explanation is supported by the limited effectiveness of heating and humidifying respiratory gases, as measured by rectal temperatures, in patients with accidental hypothermia (4). Whitby and Dunkin (5) found nasopharyngeal temperatures unreliable due to probe position being insufficiently insulated from external cold and gas leakage from around the endotracheal tube cuff. When measured near the endotracheal tube, nasopharyngeal temperatures may be influenced by the temperature of the endotracheal tube. Our calculations are further supported by Shanks (6) who calculated from skin and rectal temperatures a heat loss of 10 kcal/hr through the airways in surgical patients.

If the effects of cold and dry gases on heat balance are compared with other factors, their importance becomes evident and preventive measures can be taken to minimize cold stress during anesthesia and surgery. Ringer's solution infused at room temperature is equivalent to a cold stress of 16 kcal/L and blood at 4°C a cold stress of 30 kcal/L. Evaporation from exposed abdominal or thoracic organs may account for a cold stress as great as 400 kcal/hr. Radiative heat loss during the surgical preparation time may account for approximately 30 kcal. We have found that large heating blankets deliver 2.7 to 5.2 kcal/hr/°C temperature difference between the patient's core temperature and the water temperature in the blanket. Each layer of sheet between patient and blanket significantly reduced the heat transfer (7). In the patients of Stone et al (1) this would mean a transfer of approximately 10 kcal/hr, a fraction of the 75 kcal needed for maintenance of normal temperature during the 1st hour of anesthesia in group I. Although, Stone et al (1) could have used water temperatures of up to 44°C and thus more heat could have been supplied, we agree that heating blankets should not be widely used.

Cold stress can be prevented in part by heating and humidifying the respiratory gases and by heating blan-

kets. Other methods, however, are more useful, including covering the patient, especially the head, as much as possible, and heating infusion fluids. Infused fluids may be safely warmed to 42°C (38°C for blood). We suggest that researchers carefully choose temperature measurement sites and determine actual heat transfer so that paradoxes such as we have raised here may be unraveled and patient warming techniques better studied.

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REFERENCES

1. Stone DR, Downs JB, Paul WL, Perkins HM. Adult body temperature and heated humidification of anesthetic gases during general anesthesia. Anesth Analg 1981;60:736–41.
2. Colin J, Timbal J, Houdas Y, Boutelie C, Guiew JD. Computation of mean body temperature from rectal and skin temperatures. J Appl Physiol 1971;31:484–9.
3. Chalon J, Patel C, Ali M, et al. Humidity and the anesthetized patient. Anesthesiology 1979;50:195–8.
4. Bristow G. Resuscitation from cardiac arrest during accidental hypothermia (letter). Can Med Assoc J 1977;117:998–9.
5. Whitby JD, Dunkin LJ. Cerebral, oesophageal and nasopharyngeal temperatures. Br J Anaesth 1971;43:673–6.
6. Shanks CA. Humidification and loss of body heat during anaesthesia. 2. Effects in surgical patients. Br J Anaesth 1971;46:859–66.
7. Emergency Care Research Institute. Mobile hypo/hyperthermia machines and hypo/hyperthermia blankets. Health Devices 1981;10:259–78.

Central Cannulation: Difficulty with an Errant Guide Wire

To the Editor:

Cannulation of blood vessels using the modified "Seldinger technique" (1) is a common clinical procedure. Occasionally, difficulty is encountered in passing a catheter and dilator over a guide wire previously placed in the appropriate vessel.

We recently encountered an adult patient in whom an uncomplicated cannulation of the right internal jugular vein was made using the central approach (2), with a 16-gauge catheter. A 45-cm, .035-inch gauge "J" guide wire was passed through the catheter to a depth of approximately 20 cm with minimal resistance. The catheter was removed and a #11 scalpel blade was used to incise the skin alongside the wire. Thereafter, multiple attempts to advance a #8 French dilator over the wire were unsuccessful because an elastic, but firm resistance impeded advancement beyond 3 to 6 cm. To overcome this resistance, the skin and subcutaneous tissues were further prepared with a deeper incision alongside the guide wire and blunt dissection with a hemostat. Several more attempts were made at cannulation over the guide wire with the #8 French dilator, a 16-gauge soft catheter, and a 14-gauge catheter-over-needle (needle is approximately 17 gauge). Each attempt encountered elastic firm resistance, but without any unusual patient discomfort or evidence of a hematoma. The 17-gauge needle was utilized to rule out the prevertebral fascia or other subcutaneous tissue as causes of the obstruction. Also, in our own and others' testing, (J. L. Waller, personal communication, 1980) the 14-gauge catheter-over-needle does not appear to be able to shear the .035-inch guide wire.

Finally, all attempts were stopped and the J-wire was withdrawn. It was intact and undamaged except for two acute deformations in its midportion (Figure). Removal of the wire was made with gentle but firm retraction, encountering two momentary periods of increased resistance to withdrawal. The patient experienced no pain nor was there any increased bleeding from the site. An uneventful recannulation of the same vein using a more caudad approach was accomplished and a pulmonary arterial catheter was placed.

Several observations may be made from this event, but we wish to emphasize the following: (*a*) A smoothly placed internal jugular vein guide wire might not advance down the superior vena cava (SVC) as assumed. We believe our wire, after entering the internal jugular vein, took an erratic course either intravascularly (up

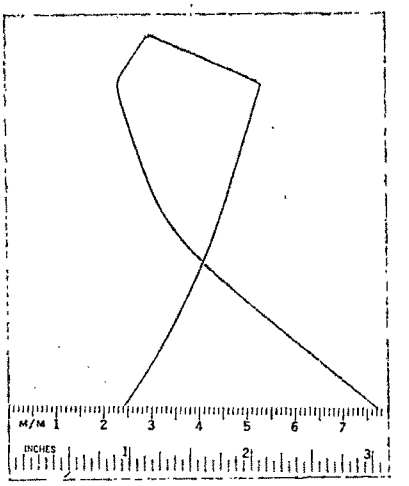


FIGURE. Deformed mid-portion of a 45-cm long, .035-inch gauge "J" guide wire.

or out a collateral vessel) or extravascularly into tissue, although the latter seemed unlikely at the time due to smooth advancement of the wire to a depth of 20 cm without patient discomfort or development of a hematoma. (*b*) The .035-inch gauge guide wire is durable and will accept abuse during a difficult cannulation with a 17-gauge needle. However, enthusiasm for such a test might best be reserved for difficult peripheral, not internal jugular or subclavian vein cannulations.

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REFERENCES

1. Seldinger SI. Catheter replacement of the needle in percutaneous arteriography: new technique. Acta Radiol 1953;39:368–76.
2. Defalque RJ. Percutaneous catheterization of the internal jugular vein. Anesth Analg 1974;53:116–21.

Nitrous Oxide at Analgesic Concentrations—An Opiate Agonist: Further Evidence

To the Editor:

The finding by Koblin et al (1) that nitrous oxide (N_2O) at analgesic (sub-

anesthetic) concentrations does not produce cross tolerance to barbiturates is an interesting one. However, the conclusion that N_2O acts at nonspecific sites is open to question. Although anesthesia may well be due to activity at nonspecific hydrophic sites (2), this may not apply to analgesia. This point further emphasizes the importance of clearly distinguishing between anesthesia and analgesia when discussing the possible mechanisms of action of various agents (3).

Although N_2O anesthesia appears to be unaffected by naloxone (4), this is not the case for analgesia. The analgesic effects of N_2O have been shown to be sensitive to naloxone at low doses in human subjects (5, 6). In addition, animal studies (7) indicate that N_2O analgesia can be reversed by both naloxone and naltrexone (7). The possibility that N_2O acts at specific opiate receptors at analgesic doses does not rest on this evidence alone. This concept is further strengthened as there appears to be cross tolerance between this agent and morphine (7), and the observation that N_2O has been shown to ameliorate opiate withdrawal symptoms (unpublished observations and reference 8). In vitro studies have demonstrated that analgesic concentrations of N_2O can displace dihydromorphine from specific binding sites indicating activity at opiate receptors (9). Furthermore, there is evidence that under certain circumstances N_2O may compete with morphine for the same receptor (10).

Therefore, the lack of cross tolerance between N_2O and barbiturates appears to give further indirect support for the concept that N_2O at analgesic concentrations acts at specific receptors.

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REFERENCES

1. Koblin DD, Deady JE, Nelson NT, Eger EI II, Bainton CR. Mice tolerant to nitrous oxide are not tolerant to barbiturates. Anesth Analg 1981;60:138–41.
2. Koblin DD, Eger EI. Theories of narcosis. N Engl J Med 1979;30:1222–4.
3. Gillman MA, Footerman DS. The need for a clearer distinction between anesthesia and analgesia in relation to the opiate system. Anesthesiology 1981;54:524.
4. Smith RA, Wilson M, Miller KW. Naloxone has no effect on nitrous oxide anesthesia. Anesthesiology 1978;49:6–8.
5. Gillman MA, Kok L, Lichtigfeld FJ. Paradoxical effect of naloxone on nitrous oxide analgesia in man. Eur J Pharmacol 1980;61: 175–7.
6. Yang JC, Clark WC, Ngai SH. Antagonism of nitrous oxide analgesia by naloxone in man. Anesthesiology 1980;52:414–7.
7. Berkowitz BA, Ngai SH, Finck AD. Nitrous oxide "analgesia" resemblance to opiate action. Science 1976;194:967–9.
8. Kripke BJ, Hechtman HB. Nitrous oxide for pentazocine addiction and for intractable pain: report of a case. Anesth Analg 1972;51: 520–7.
9. Ahmed MS, Byrne WL. Opiate receptor binding studies: influence of a reversible sulfhydryl agent. In: Way EL, ed. Endogenous and exogenous opiate agonists and antagonists. New York: Pergamon, 1980:51–4.
10. Gillman MA, Lichtigfeld FJ. The similarity of the action of nitrous oxide and morphine. Pain 1981;10:110.

To the Editor:

As Dr. Gillman states, naloxone antagonizes nitrous oxide analgesia (1) but not nitrous oxide anesthesia (2), and it is therefore important to distinguish between the measurements of analgesic and anesthetic potencies (3). However, examination of cross tolerance between nitrous oxide and other anesthetics has been performed using a single test (abolishment of righting reflex) for anesthetic potency. Mice continuously exposed to subanesthetic (analgesic) concentrations of 50% nitrous oxide for 3 weeks have an increased requirement for nitrous oxide, cyclopropane, isoflurane, and ethanol (4, 5), implying that these agents share a common mechanism of anesthetic action. In contrast, a significant cross tolerance cannot be detected between nitrous oxide and three different barbiturates (6).

The differences in structure between nitrous oxide, cyclopropane, and isoflurane suggest that these anesthetics do not interact with a single specific receptor site. However, the excellent correlation between lipid solubility and potency for these and other inhaled anesthetics implies a common hydrophobic site of anesthetic action (7). Nevertheless minor deviations from this correlation do exist (8, 9), and the potency of an agent may depend on specific interactions in addition to lipid solubility. Indeed, the lack of a simple correlation between anesthetic potency and the alteration of membrane lipid properties have led others to postulate that anesthetics act at specific target sites (10, 11). At present there is only indirect support for such specific sites of anesthetic and analgesic action. The definitive experiments, those of biochemical isolation of specific receptors and the demonstration of high affinity anesthetic binding sites, remain to be performed.

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REFERENCES

1. Yang JC, Clark WC, Ngai SH. Antagonism of nitrous oxide analgesia by naloxone in man. Anesthesiology 1980;52:414–7.
2. Smith RA, Wilson M, Miller KW. Naloxone has no effect on nitrous oxide anesthesia. Anesthesiology 1978;49:6–8.
3. Gillman MA, Footerman DS. The need for a clearer distinction between anesthesia and analgesia in relation to the opiate system. Anesthesiology 1981;54:524.
4. Smith RA, Winter PM, Smith M, Eger EI II. Tolerance to and dependence on inhalational anesthetics. Anesthesiology 1979;50: 505–9.
5. Koblin DD, Deady JE, Dong DE, Eger EI II. Mice tolerant to nitrous oxide are also tolerant to alcohol. J Pharmacol Exp Ther 1980;213:309–12.
6. Koblin DD, Deady JE, Nelson NT, Eger EI II, Bainton CR. Mice tolerant to nitrous oxide are not tolerant to barbiturates. Anesth Analg 1981;60:138–41.
7. Koblin DD, Eger EI II. How do inhaled anesthetic work? In: Miller RD, ed. Anesthesia. New York: Churchill Livingstone, vol 1, 1981:283–308.
8. Koblin DD, Eger EI II, Johnson BH, et al. Minimum alveolar concentrations and oil/gas partition coefficients of four anesthetic isomers. Anesthesiology 1981;54:314–7.
9. Koblin DD, Eger EI II, Johnson BH, Collins P, Terrell RC, Speers L. Are convulsant gases also anesthetics? Anesth Analg 1981;60:464–70.
10. Richards CD, Martin K, Gregory S, et al. Degenerate perturbations of protein structure as the mechanism of anesthetic action. Nature 1978;276:775–9.
11. Franks NP, Lieb WR. Is membrane expansion relevant to anesthesia? Nature 1981;292: 248–51.

Epinephrine and Duration of Spinal Anesthesia

To the Editor:

We read with interest the article by Chambers et al (1) reporting that the

addition of varying amounts of epinephrine did not result in clinically useful prolongation of lidocaine-induced spinal anesthesia. These findings contradict earlier observations made by other investigators (2–4). This difference could reflect a smaller study group plus a greater mean age of patients studied by Chambers et al (1). For example, Park et al (2) observed significant variations in the duration of subarachnoid anesthesia in 222 patients when they were given the same amount of local anesthetic with or without epinephrine. It is possible that individual variations in neural response cannot be eliminated when small groups of patients are studied. In their clinical study, Bonica et al (3) had the unusual opportunity to administer spinal anesthesia to 48 patients who had a similar surgical procedure performed more than once within a few days. By studying the same patients they could minimize individual variations in drug absorption and neural sensitivity. In those patients (who served as their own control) Bonica et al observed a 48% prolongation of the duration of objective sensory anesthesia (T-10 level) with the addition of epinephrine. In the study by Chambers et al, the mean age of the patients was 65 years, whereas in all other studies, mean age was less than 50 years (2–4). Conceivably, atherosclerotic small arterioles in older patients may not respond as well to the surface application of epinephrine as they may in younger patients. Perhaps an older patient population could explain the absence of differences in the duration of sensory block with the addition of varying amounts of epinephrine. Indeed, Egbert et al (4) in a younger group of patients (44 years of age) noted progressive prolongation of spinal anesthesia with the use of increasing amounts of epinephrine. Finally, Giasi et al (5) observed that 15 minutes following subarachnoid injection of lidocaine the blood level was as high as was noted following the injection of the same amount of drug into the more vascular epidural space. It seems likely that epinephrine would remain in the subarachnoid space for 15 minutes following its administration and decrease the absorption of lidocaine from that space and thereby prolong the duration of anesthesia.

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REFERENCES

1. Chambers WA, Littlewood DG, Logan MR, Scott DB. Effect of added epinephrine on spinal anesthesia with lidocaine. Anesth Analg 1981;60:417–20.
2. Park WY, Balingit PE, McNamara TE. Effects of patient age, pH of cerebrospinal fluid, and vasopressors on onset and duration of spinal anesthesia. Anesth Analg 1975;54:455–7.
3. Bonica JJ, Backup PH, Pratt WH. The use of vasoconstrictors to prolong spinal anesthesia. Anesthesiology 1950;12:431–40.
4. Egbert LD, Deas TC. Effect of epinephrine upon the duration of spinal anesthesia. Anesthesiology 1960;21:345–7.
5. Giasi RM, D'Agostino E, Covino BG. Absorption of lidocaine following subarachnoid and epidural administration. Anesth Analg 1979;58:360–3.

To the Editor:

Although the recent literature has generally agreed that epinephrine substantially prolongs spinal anesthesia, this has not always been the case. Pitkin felt that epinephrine was often ineffective intrathecally because it was rapidly destroyed. Whatever the merits of his theory, it was presumably based on the observation of its ineffectiveness.

The studies described by Ravindran et al did indeed involve greater numbers of patients but they were poorly controlled and not blind. We feel that meaningful results can only be obtained from carefully controlled studies in which the assessment of sensory loss is carried out at prescribed intervals by an observer who is unaware of the solution used in individual cases. Ideally all the assessments should be carried out by the same person. Obviously the numbers of patients studied under such conditions will be smaller than in less well controlled studies. In Edinburgh we have now reported studies involving more than 300 patients (all in groups of 10). There are several groups of patients, from different studies, who have received the same solutions. The results for those groups who received the same solutions are similar. We do not accept that greater numbers alone imply more meaningful results.

Another problem is that of deciding suitable end points when comparing the duration of different solutions. Various investigators have used at least 10 different criteria for the "duration" of block, and often one gets the impression that only those that showed the expected differences are presented.

It is conceivable that older patients may respond differently although we are not aware of any suggestions that epinephrine is less effective in the elderly in prolonging neural blockade in other sites.

We would reemphasize that our results did show an increase in mean duration when epinephrine was added. What the results did not show was that this prolongation of effect was either marked or clinically useful. In a later study (1) we have noted that added vasoconstrictors occasionally produce prolonged spinal blocks—a feature that was also present in our initial study—and this may be responsible for the clinical impression that vasoconstrictors significantly prolong spinal anesthesia. However, with solutions of lidocaine or bupivacaine in dextrose, such additions cannot be relied upon to produce a significant prolongation in an individual patient.

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1. Chambers WA, Littlewood DG, Scott DB. Spinal anesthesia with hyperbaric bupivacaine: effect of added vasoconstrictors, Anesth Analg 1982;61:49–52.

book REVIEWS

Coagulation: The Essentials, by D. P. Fischbach and R. P. Fogdall, Baltimore, The Williams & Wilkins Co., 1981, 252 pp, $19.00.

The authors of this book are the first to write a basic text for nonexperts in the field of coagulation and hemostasis that discusses a difficult subject in a manner that is not only easy to read, but is also understandable. In the introduction the authors state that the "book provides a framework to help the reader organize, catalog, remember and use the fundamental facts of hemostasis." This text more than accomplishes its stated purpose.

The text is unique in presentation. Each of the nine chapters discusses only four common topics: vascular integrity, platelets, the coagulation cascade, and clot lysis. The authors limit each chapter to the same four topics for purposes of "organization and ease of comprehension." Chapters of note include "Basics of Clotting and Lysis," "Coagulation Testing," "Disorders of Coagulation," and "Analysis and Treatment of the Bleeding Patient." At the bottom of each page are questions or key phrases which the authors state are for "review and further emphasis." These questions are merely repetitions of the main text and, along with the abundance of illustrations, serve to help the reader retain and comprehend more of the subject matter. Upon finishing the book, I was amazed that there were few, if any, topics in the text that could or would confuse the average reader.

The authors correctly note that because of their unique presentation, i.e., four common topics per chapter, many "fascinating areas of coagulation cannot be covered fully." They have, however, partially compensated for this by including an appendix that addresses some specific areas. Of interest to anesthesiologists are sections on coagulation problems associated with cardiopulmonary bypass and use of the ACT (activated coagulation time) as a guide to heparin and protamine therapy.

The authors of this text have written an excellent book on a subject that many find difficult not only to understand but also to retain. Their book is not only easy to understand, but its manner of presentation makes the subject matter retainable. This book is recommended for all anesthesia students, anesthesiologists, and critical care physicians.

Stephen M. Brzica, MD
Assistant Professor of Anesthesia
University of Minnesota
Minneapolis, MN

Brain Failure and Resuscitation, edited by A. Grenvik and P. Safar, New York, Churchill Livingstone, 1981, 268 pp, $37.50.

This book is an excellent example of all that's good and all that's bad in a multiauthored publication. This can be anticipated as soon as one examines the list of contributors, for they range from internationally recognized experts to virtual unknowns. In general, the quality of the chapter varies in direct relationship to the reputation of the contributor. Accordingly, the selective reader will find more than 50% of this book to be useful and informative. The chapters concerned with the basic pathophysiology of brain failure secondary to ischemia, although at times cursory, are reasonably current and provide a good overview of the topic. For the clinician, the chapters concerned with the clinical evaluation, radiologic evaluation, and monitoring of the patient with brain damage can be readily recommended.

Thereafter, this book is a bit of a grab bag which fails to deliver that promised by the title: useful information concerned with brain resuscitation. This should not be surprising. The subject of brain resuscitation is in its infancy and at this time it is unknown whether maturity will ever be achieved. In the preface the editors express hope that this book "leaves the reader with the impression that the brain has emerged from its 'black box' status." Alas, it does not. Instead one is confronted with chapters presenting a morass of speculation, incomplete information, and at times misinformation concerned with brain "resuscitation." Reading this is akin to examining the horizon with an out-of-focus telescope. This is exemplified by at least one such chapter wherein most of the references are misnumbered in the text. The final chapter dealing with "decision-making" in brain death leaves the reader decidedly undecided as to what should be done. This again is not surprising because, as with brain resuscitation, there is simply insufficient objective data to permit any firm recommendations.

On balance, this book will confuse and even mislead the naive student or trainee who is looking for information concerned with brain ischemia and resuscitation. For the well grounded, critical, mature practitioner, there is much useful information which can be obtained by selective reading.

John D. Michenfelder, MD
Professor of Anesthesiology
Mayo Medical School
Rochester, MN

Ambulatory Health Services in America: Past, Present and Future, by M. I. Roemer, Rockville, MD, Aspen Systems Corp., 1981, 468 pp, $33.50.

The objective of this readable book is clearly stated: "to examine the attributes of this organizational process and where it is heading." The history of the development of health care from a one-to-one encounter between patient and physician to "organized ambulatory health service" is traced in a detailed, logical, well documented, and scholarly manner. Separate chapters are devoted to hospital outpatient departments, public health clinics, school and college health services, industrial health units, private group medical practice, special government-financed clinics, special voluntary clinics, clinics according to purpose, and clinics of health maintenance organizations. Each of these chapters has a historical and a general overview section, and most of these chapters end with a statistical evaluation of each type of clinic in Los Angeles County in the early 1970s. In essence, the growth of socialized health care in the United States and the world is traced.

As the content is more socioeconomic than scientific, the book should be primarily of interest to sociologists, administrators, and politicians and is unlikely to be read in its entirety by practicing physicians. Certainly there is little of interest for anesthesiologists, except the prediction that future ambulatory health services will be delivered by public health agencies.

John W. Pender, MD
Emeritus Professor of
Clinical Anesthesia
Stanford University
Stanford, CA

Handbook of Percutaneous Central Venous Catheterisation, by M. Rosen, I. P. Latto, and W. Shang, Philadelphia, W. B. Saunders Co. Ltd., 1981, 134 pp, $28.00.

This handbook fulfills the criteria for such, as it is a concise account of a particular topic and it can easily be carried around. The stated aim of the book is to bring together the major methods of percutaneous central venous catheterization into a practical form using a systematic format and illustrating each technique by diagrams. The authors are successful in this but the result is a book that cannot be read enjoyably from cover to cover. Rather, it provides a readily accessible account of many techniques necessary to provide cannulation of the central venous system. In this way, it is an excellent reference which should be of value to those learning the art of central venipuncture, those who wish to refresh such knowledge, those who wish to attempt an alternative technique, and finally, those who require an extensive and well referenced account of the topic. I believe this book should be in the library of any institution in which percutaneous central venous catheterization is practiced.

John C. McMichan, MBBS, PhD
Assistant Professor
of Anesthesiology
Mayo Medical School
Rochester, MN

BOOKS RECEIVED

Self-Assessment of Current Knowledge for the Nurse Anesthetist, by A. R. Bakutis, Garden City, NY, Medical Examination Publishing Co, Inc, 1981, 235 pp, $15.00.

Critical Care for Surgical Patients, edited by J. M. Beal, New York, Macmillan Publishing Co, Inc, 1982, 606 pp, $45.00.

Pathophysiology of Shock, Anoxia, and Ischemia, edited by R. A. Cowley and B. E. Trump, Baltimore, The Williams & Wilkins Co, 1982, 710 pp, $75.00.

A Basis and Practice of Neuroanaesthesia, Second Edition, edited by E. Gordon, New York, American Elsevier Publishing Co, Inc, 1981, 354 pp, $87.75.

Adverse Reactions to Anaesthetic Drugs, edited by J. A. Thornton, New York, American Elsevier Publishing Co, Inc, 1981, 336 pp, $97.00.

A Guide for Authors

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   Anonymous. Epidemiology for primary health care. Int J Epidemiol 1976;5:224–5.

Books and Other Monographs

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   Osler AG. Complement: mechanisms and functions. Englewood Cliffs: Prentice-Hall, 1976.

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5. Editor, Compiler, Chairman as Author

   Rhodes AJ, Van Rooyen CE, comps. Textbook of virology: for students and practitioners of medicine and the other health sciences. 5th ed. Baltimore: Williams & Wilkins, 1968.

6. Chapter in Book

   Weinstein L, Swartz MN. Pathogenic properties of invading microorganisms. In: Sodeman WA Jr, Sodeman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: WB Saunders, 1974:457–72.

7. Agency Publication

   National Center for Health Statistics. Acute conditions: incidence and associated disability, United States July 1968–June 1969. Rockville, Md.: National Center for Health Statistics, 1972. (Vital and health statistics. Series 10: Data from the National Health Survey, no. 69) (DHEW publication no. (HSM)72-1036).

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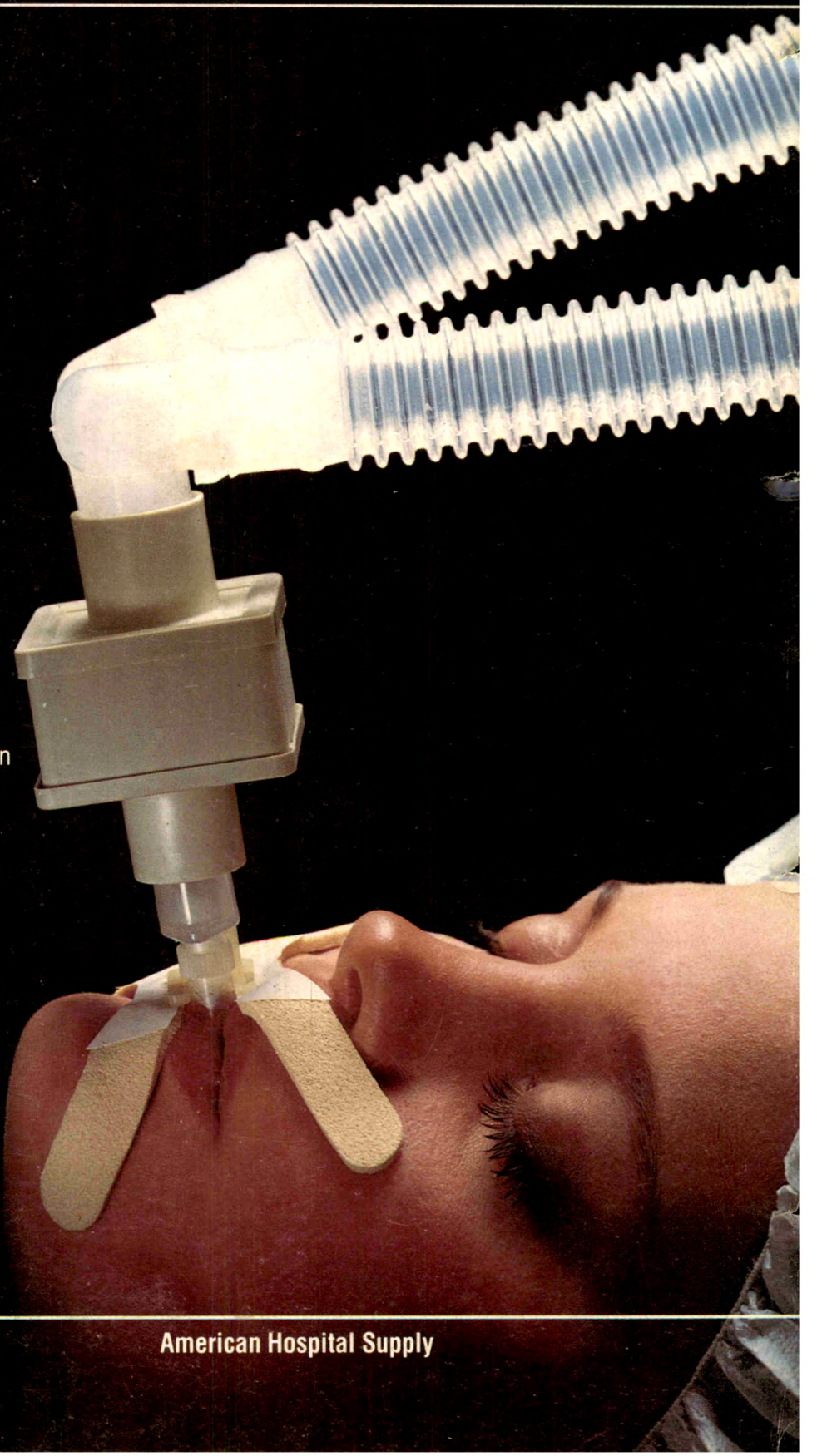
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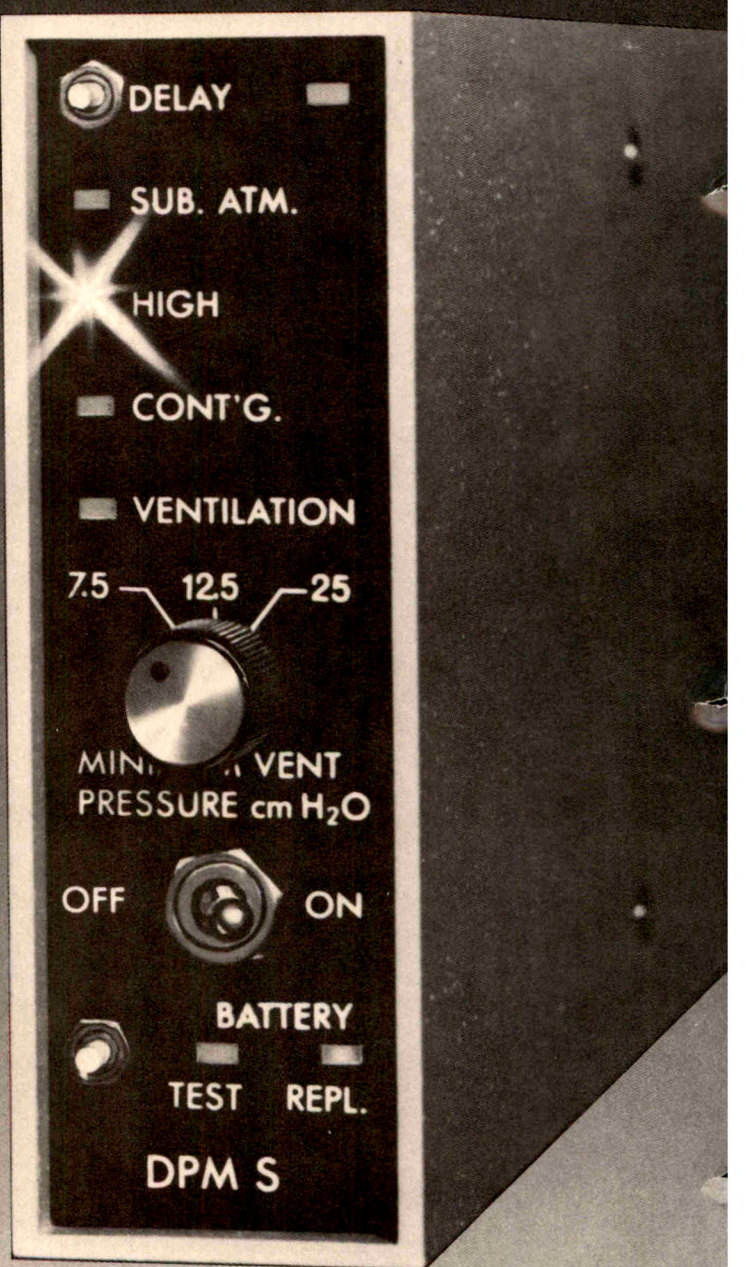


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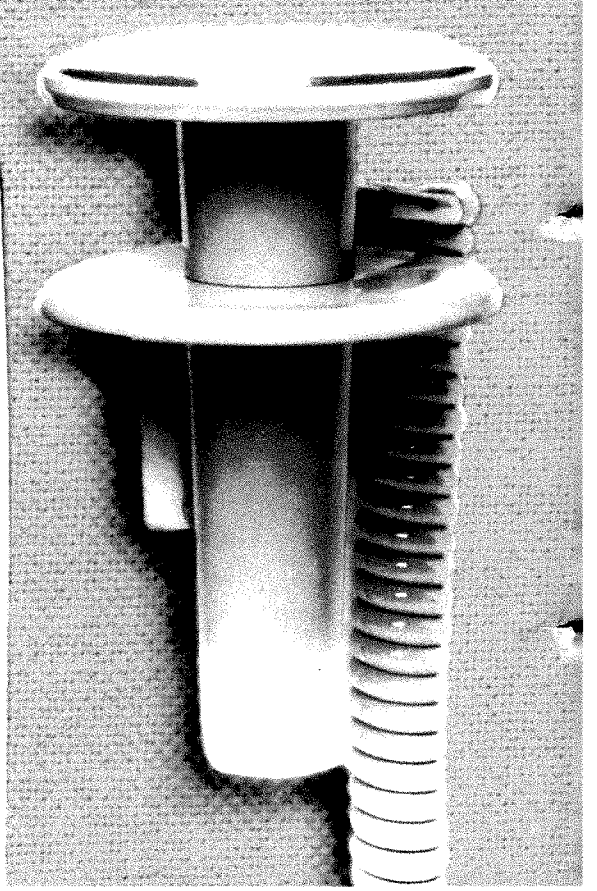
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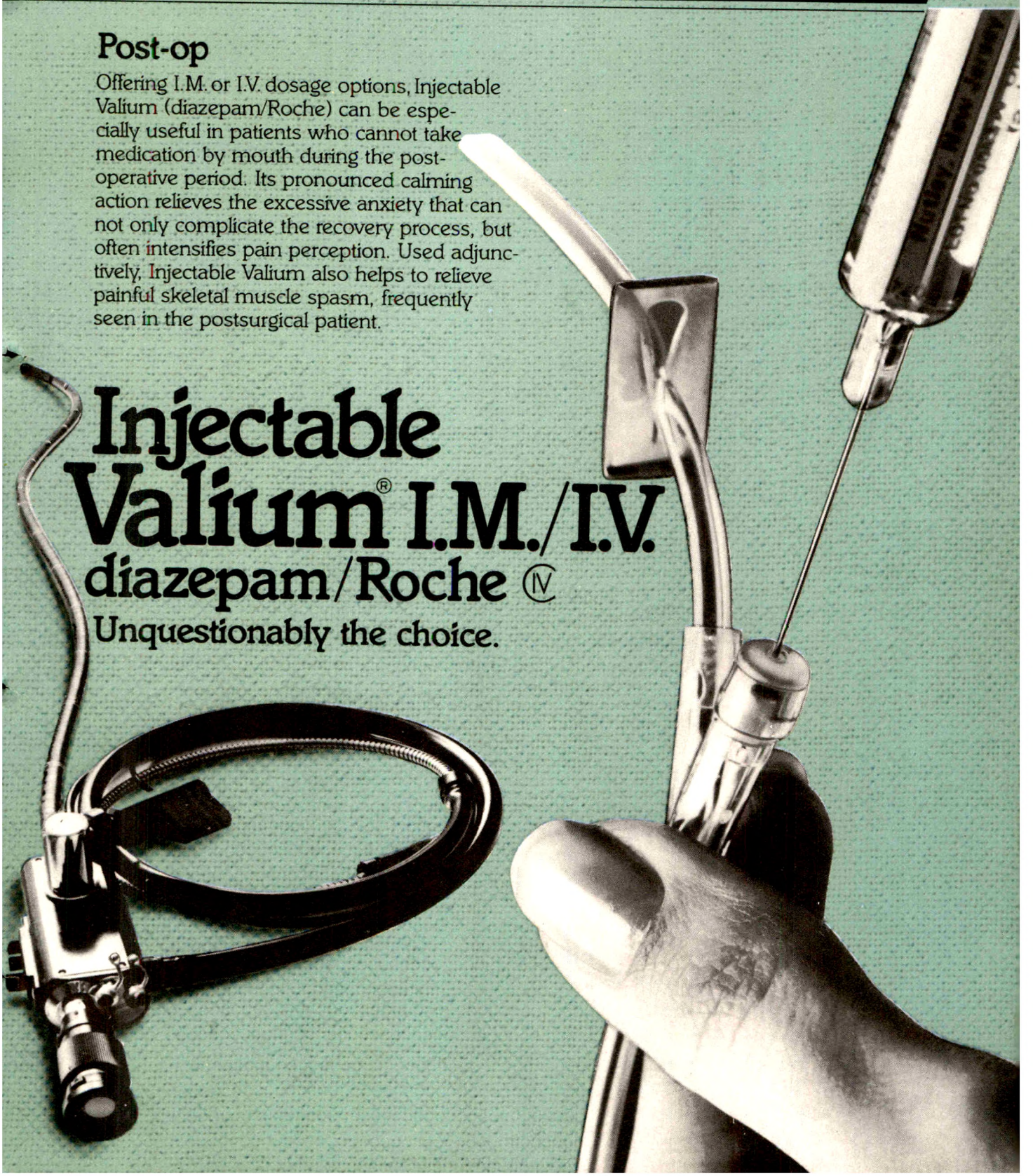
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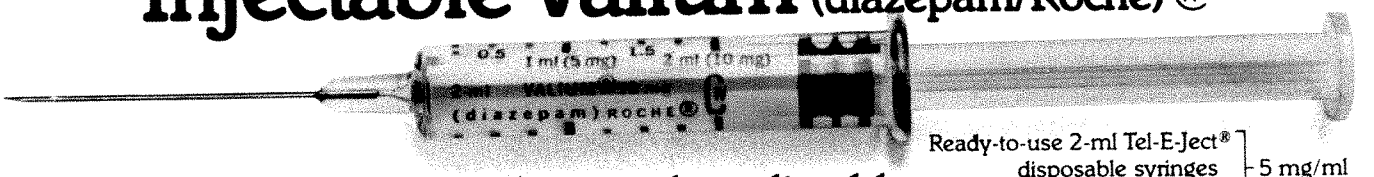
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Indications: Management of anxiety disorders, or short-term relief of symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic. Symptomatic relief of acute agitation, tremor, impending or acute delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in: relief of skeletal muscle spasm due to reflex spasm to local pathology; spasticity caused by upper motor neuron disorders; athetosis; stiff-man syndrome; tetanus; status epilepticus, severe recurrent seizures; adjunctively in anxiety, tension or acute stress reactions prior to endoscopic/surgical procedures; cardioversion.

Contraindications: Hypersensitivity; acute narrow angle glaucoma; may be used in paitents with open angle glaucoma receiving appropriate therapy.

Warnings: *To reduce the possibility of venous thrombosis, phlebitis, local irritation, swelling, and, rarely, vascular impairment when used I.V.: inject slowly, taking at least one minute for each 5 mg (1 ml) given; do not use small veins, i.e., dorsum of hand or wrist; use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute Valium (diazepam/Roche) with other solutions or drugs in syringe or infusion flask. If it is not feasible to administer Valium directly I.V., it may be injected slowly through the infusion tubing as close as possible to the vein insertion.*

Administer with extreme care to elderly, very ill, those with limited pulmonary reserve because of possibility of apnea and/or cardiac arrest; concomitant use of barbiturates, alcohol or other CNS depressants increases depression with increased risk of apnea; have resuscitative facilities available. When used with narcotic analgesic, eliminate or reduce narcotic dosage at least ⅓, administer in small increments. Should not be administered to patients in shock, coma, acute alcoholic intoxication with depression of vital signs. As with most CNS-acting drugs, caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).

Has precipitated tonic status epilepticus in patients treated for petit mal status or petit mal variant status.

Withdrawal symptoms similar to those with barbiturates and alcohol have been observed with abrupt discontinuation after long use of excessive doses. Infrequently, milder withdrawal symptoms have been reported following abrupt discontinuation of benzodiazepines after long, continuous use at high therapeutic levels. After extended therapy, gradually taper dosage.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations, as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Not recommended for OB use.

Efficacy/safety not established in neonates (age 30 days or less); prolonged CNS depression observed. In children, give slowly (up to 0.25 mg/kg over 3 minutes) to avoid apnea or prolonged somnolence; can be repeated after 15 to 30 minutes. If no relief after third administration, appropriate adjunctive therapy is recommended.

Precautions: Although promptly controlled, seizures may return; readminister if necessary; not recommended for long-term maintenance therapy. If combined with other psychotropics or anticonvulsants, carefully consider individual pharmacologic effects—particularly with known compounds which may potentiate action of Valium (diazepam/Roche), *i.e.*, phenothiazines, narcotics, barbiturates, MAO inhibitors, antidepressants. Protective measures indicated in highly anxious patients with accompanying depression who may have suicidal tendencies. Observe usual precautions in impaired hepatic function; avoid accumulation in patients with compromised kidney function. Laryngospasm/increased cough reflex are possible during peroral endoscopic procedures; use topical anesthetic, have necessary countermeasures available. Hypotension or muscular weakness possible, particularly when used with narcotics, barbiturates or alcohol. Use lower doses (2 to 5 mg) for elderly/debilitated.

The clearance of Valium and certain other benzodiazepines can be delayed in association with Tagamet (cimetidine) administration. The clinical significance of this is unclear.

Adverse Reactions: Drowsiness, fatigue, ataxia, venous thrombosis/phlebitis at injection site, confusion, depression, dysarthria, headache, hypoactivity, slurred speech, syncope, tremor, vertigo, constipation, nausea, incontinence, changes in libido, urinary retention, bradycardia, cardiovascular collapse, hypotension, blurred vision, diplopia, nystagmus, urticaria, skin rash, hiccups, changes in salivation, neutropenia, jaundice. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Cough, depressed respiration, dyspnea, hyperventilation, laryngospasm/pain in throat and chest have been reported in peroral endoscopic procedures. Isolated reports of neutropenia, jaundice; periodic blood counts, liver function tests advisable during long-term therapy. Minor EEG changes, usually low-voltage fast activity, of no known significance.

Dosage: Usual initial dose in older children and adults is 2 to 20 mg I.M. or I.V., depending on indication and severity. Larger doses may be required in some conditions (tetanus). In acute conditions injection may be repeated within 1 hour, although interval of 3 to 4 hours is usually satisfactory. Lower doses (usually 2 to 5 mg) with slow dosage increase for elderly or debilitated patients and when sedative drugs are added. (See Warnings and Adverse Reactions.)

For dosages in infants and children see below; have resuscitative facilities available.

I.M. use: by deep injection into the muscle.

I.V. use: inject slowly, take at least one minute for each 5 mg (1 ml) given. Do not use small veins, i.e., dorsum of hand or wrist. Use extreme care to avoid intra-arterial administration or extravasation. Do not mix or dilute Valium (diazepam/Roche) with other solutions or drugs in syringe or infusion flask. If it is not feasible to administer Valium directly I.V., it may be injected slowly through the infusion tubing as close as possible to the vein insertion.

Moderate anxiety disorders and symptoms of anxiety, 2 to 5 mg I.M. or I.V. and severe anxiety disorders and symptoms of anxiety, 5 to 10 mg I.M. or I.V., repeat in 3 to 4 hours if necessary; acute alcoholic withdrawal, 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary. Muscle spasm, in adults, 5 to 10 mg I.M. or I.V. initially, then 5 to 10 mg in 3 to 4 hours if necessary (tetanus may require larger doses); in children, *administer I.V. slowly;* for tetanus in infants over 30 days of age, 1 to 2 mg I.M. or I.V., repeat every 3 to 4 hours if necessary; in children 5 years or older 5 to 10 mg repeated every 3 to 4 hours as needed. Respiratory assistance should be available.

Status epilepticus, severe recurrent convulsive seizures (I.V. route preferred), 5 to 10 mg adult dose administered slowly, repeat at 10- to 15-minute intervals up to 30 mg maximum. Repeat in 2 to 4 hours if necessary keeping in mind possibility of residual active metabolites. Use caution in presence of chronic lung disease or unstable cardiovascular status. Infants (over 30 days) and children (under 5 years), 0.2 to 0.5 mg slowly every 2 to 5 min., up to 5 mg (I.V. preferred). Children 5 years plus, 1 mg every 2 to 5 min., up to 10 mg (slow I.V. preferred); repeat in 2 to 4 hours if needed.

EEG monitoring may be helpful.

In endoscopic procedures, titrate I.V. dosage to desired sedative response, generally 10 mg or less but up to 20 mg (if narcotics are omitted) immediately prior to procedure; if I.V. cannot be used, 5 to 10 mg I.M. approximately 30 minutes prior to procedure. As preoperative medication, 10 mg I.M.; in cardioversion, 5 to 15 mg I.V. within 5 to 10 minutes prior to procedure. Once acute symptomatology has been properly controlled with injectable form, patient may be placed on oral form if further treatment is required.

Management of Overdosage: Manifestations include somnolence, confusion, coma, diminished reflexes. Monitor respiration, pulse, blood pressure; employ general supportive measures, I.V. fluids, adequate airway. Hypotension may be combated by the use of levarterenol or metaraminol. Dialysis is of limited value.

Supplied: Ampuls, 2 ml, boxes of 10; Vials, 10 ml, boxes of 1; Tel-E-Ject® (disposable syringes), 2 ml, boxes of 10. Each ml contains 5 mg diazepam compounded with 40% propylene glycol, 10% ethyl alcohol, 5% sodium benzoate and benzoic acid as buffers, and 1.5% benzyl alcohol as preservative.

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An economical, single-trace instrument designed for ECG measurement. The Vitatek 408 provides heart-rate reading (triggered sweep), with high and low heart-rate alarms. There is three-lead selection and full lead is optional. It's compact, lightweight, battery and line (AC) operable — extremely portable. An optional recorder is available.



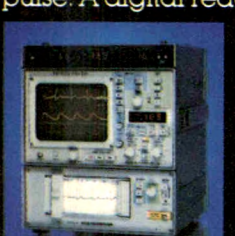
The Vitatek 413A Neonatal Monitor

A three-trace instrument designed especially for neonatal monitoring. It simultaneously displays ECG, blood pressure or peripheral pulse, and respiration waveforms. A selectable digital readout shows heart rate, respiration rate, systolic/diastolic or mean blood pressure, two temperatures or temperature difference. An optional recorder is available in addition to a digital readout module.



The Vitatek 414 Adult Monitor

A dual or three-trace monitor with simultaneous display of ECG and blood pressure or peripheral pulse. A digital readout shows heart rate, systolic/diastolic blood pressures, mean blood pressure or temperature. Options are available for pressure gauge factor, ECG full-lead select, electrosurgical suppression, recorder and digital readout module.



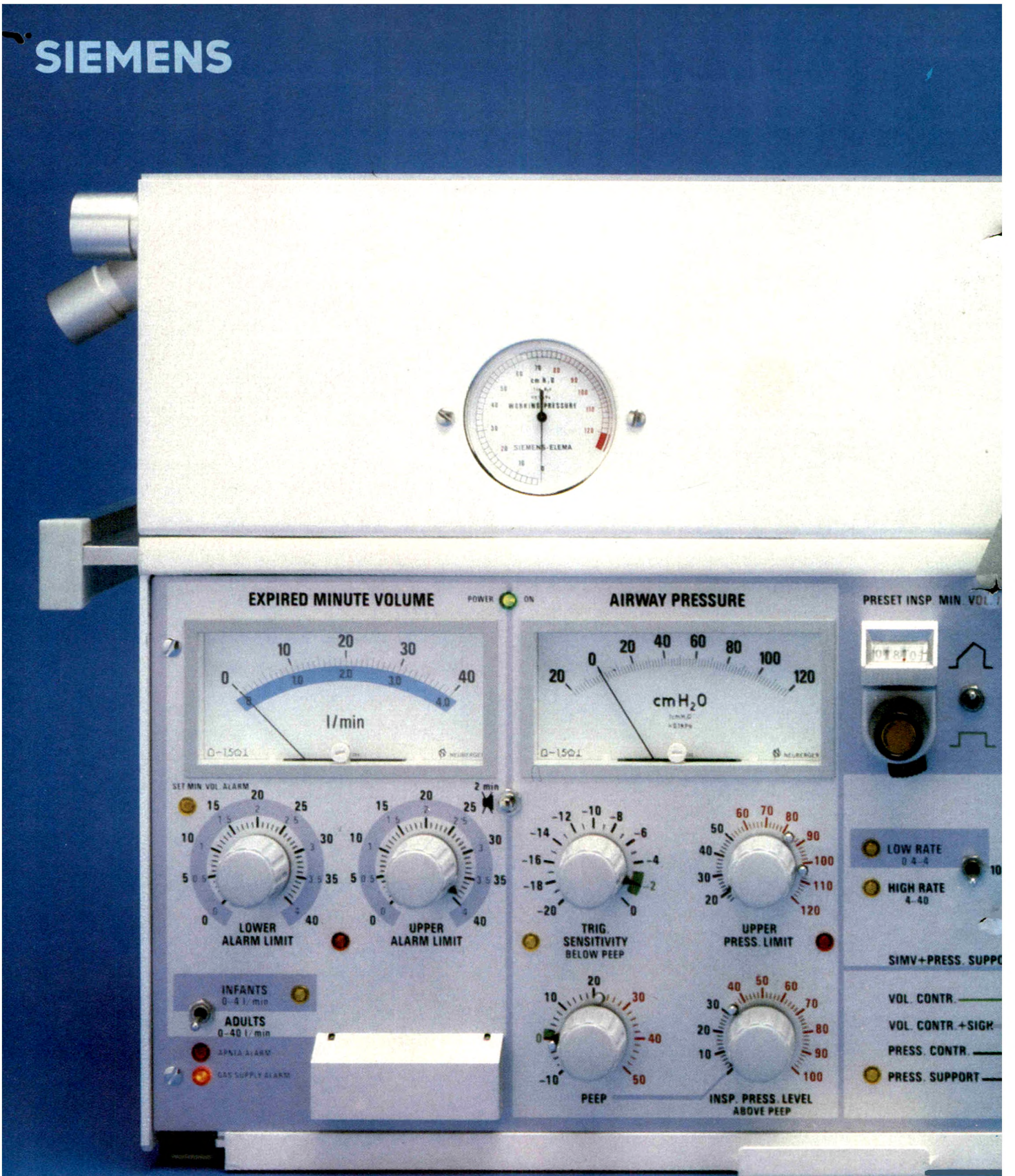
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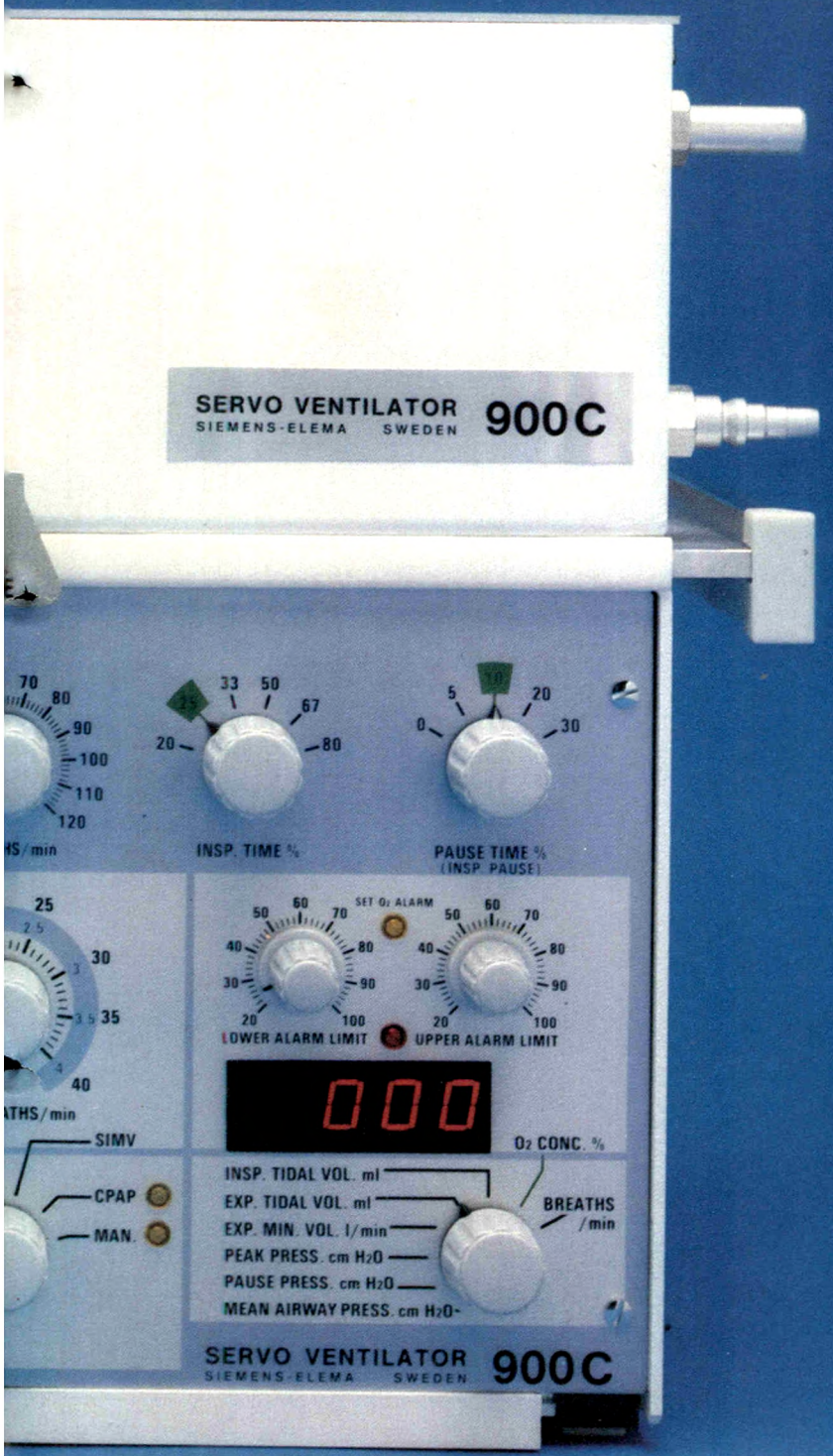
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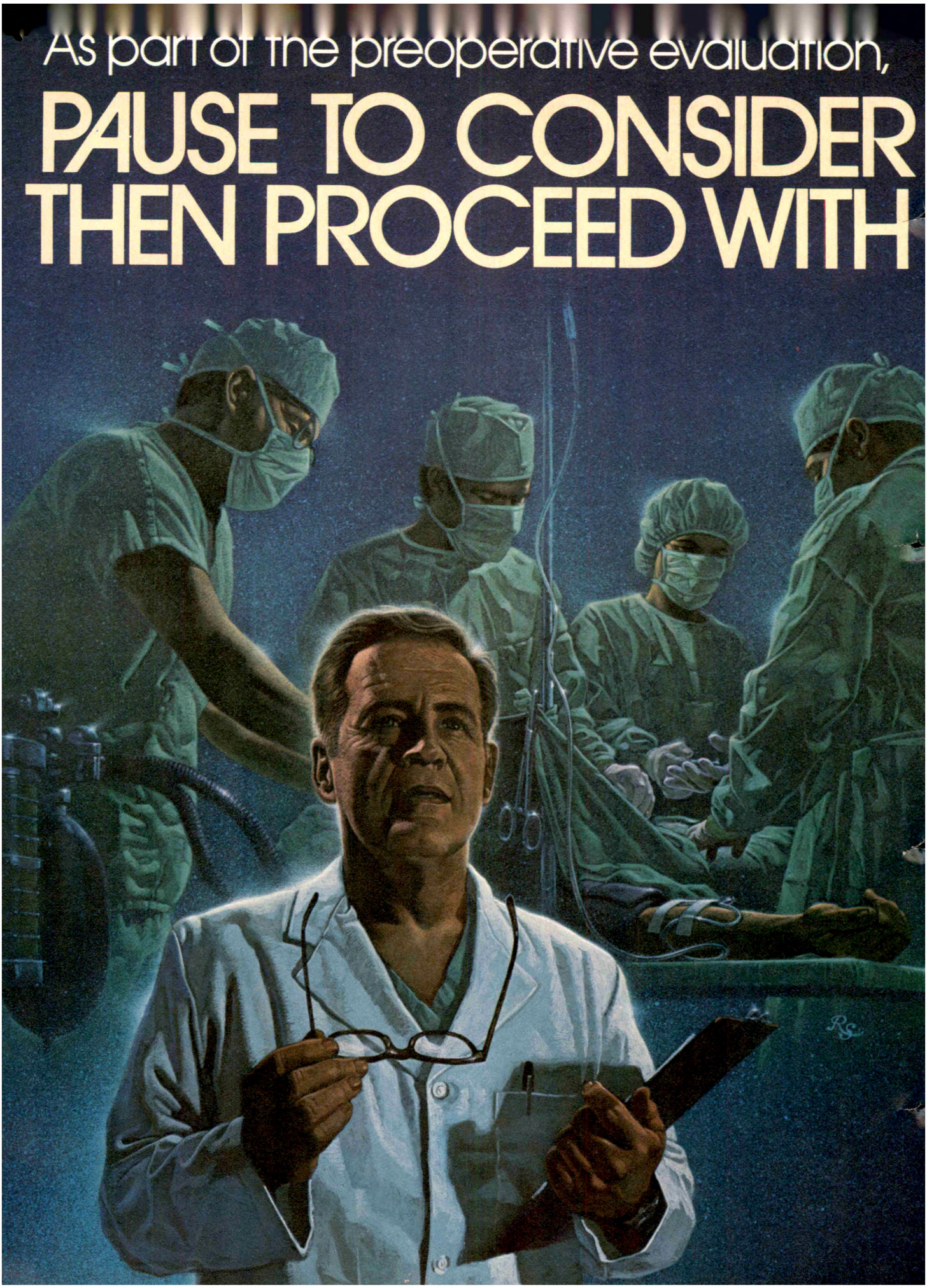
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PAVULON®
(pancuronium bromide injection)

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A Record of Success

PAVULON® nondepolarizing muscle relaxant (pancuronium bromide injection)

BRIEF SUMMARY
(Please consult package insert for full prescribing information.)

THIS DRUG SHOULD ONLY BE ADMINISTERED BY ADEQUATELY TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

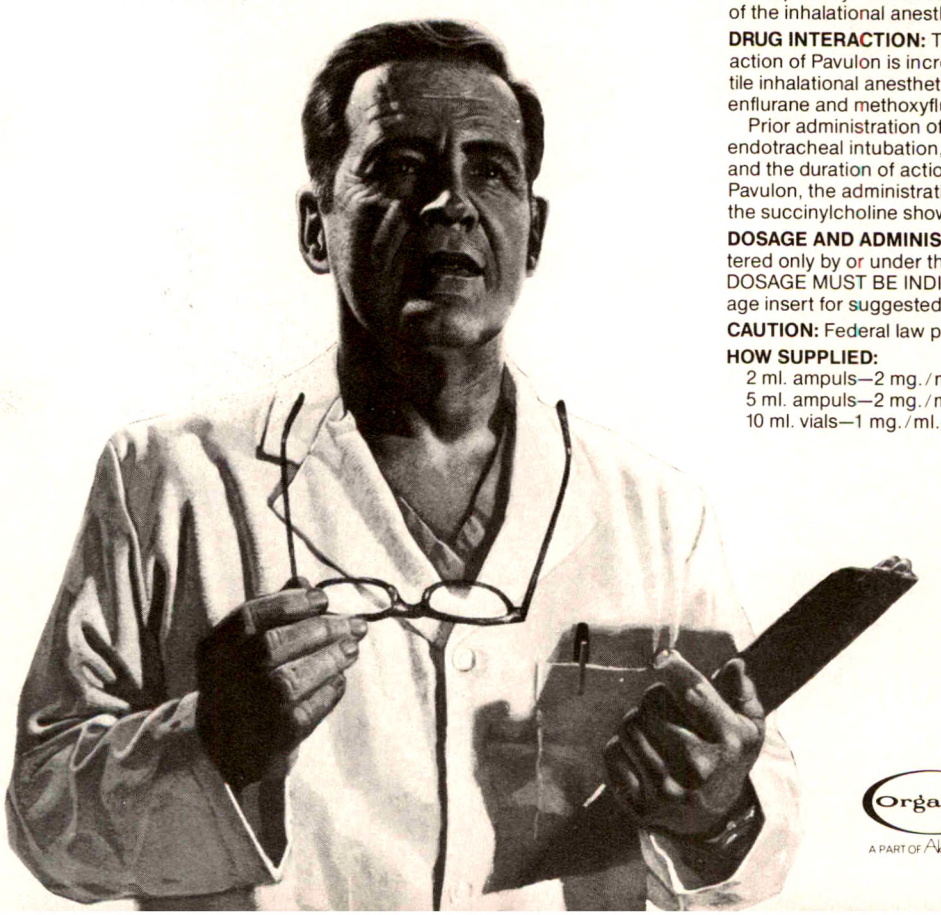
ACTIONS: Pavulon is a non-depolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform) on the myoneural junction.

Pavulon (pancuronium bromide) is antagonized by acetylcholine, anticholinesterases, and potassium ion. Its action is increased by inhalational anesthetics such as halothane, diethyl ether, enflurane and methoxyflurane, as well as quinine, magnesium salts, hypokalemia, some carcinomas, and certain antibiotics such as neomycin, streptomycin, clindamycin, kanamycin, gentamicin and bacitracin. The action of Pavulon may be altered by dehydration, electrolyte imbalance, acid-base imbalance, renal disease, and concomitant administration of other neuromuscular agents.

CONTRAINDICATIONS: Pavulon is contraindicated in patients known to be hypersensitive to the drug or to the bromide ion.

WARNINGS: PAVULON SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS, WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION.

In patients who are known to have myasthenia gravis small doses of Pavulon may have profound effects. A peripheral nerve stimulator is especially valuable in assessing the effects of Pavulon in such patients.



USAGE IN PREGNANCY: The safe use of pancuronium bromide has not been established with respect to the possible adverse effects upon fetal development. Therefore, it should not be used in women of childbearing potential and particularly during early pregnancy unless in the judgment of the physician the potential benefits outweigh the unknown hazards.

Pavulon may be used in operative obstetrics (Cesarean section), but reversal of pancuronium may be unsatisfactory in patients receiving magnesium sulfate for toxemia of pregnancy, because magnesium salts enhance neuromuscular blockade. Dosage should usually be reduced, as indicated, in such cases.

PRECAUTIONS: Although Pavulon has been used successfully in many patients with pre-existing pulmonary, hepatic, or renal disease, caution should be exercised in these situations. This is particularly true of renal disease since a major portion of administered Pavulon is excreted unchanged in the urine.

ADVERSE REACTIONS: Neuromuscular: the most frequently noted adverse reactions consist primarily of an extension of the drug's pharmacological actions beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle relaxation resulting in respiratory insufficiency or apnea. Inadequate reversal of the neuromuscular blockade by anticholinesterase agents has also been observed with Pavulon (pancuronium bromide) as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate.

Cardiovascular: A slight increase in pulse rate is frequently noted.

Gastrointestinal: Salivation is sometimes noted during very light anesthesia, especially if no anticholinergic premedication is used.

Skin: An occasional transient rash is noted accompanying the use of Pavulon.

Respiratory: One case of wheezing, responding to deepening of the inhalational anesthetic, has been reported.

DRUG INTERACTION: The intensity of blockade and duration of action of Pavulon is increased in patients receiving potent volatile inhalational anesthetics such as halothane, diethyl ether, enflurane and methoxyflurane.

Prior administration of succinylcholine, such as that used for endotracheal intubation, enhances the relaxant effect of Pavulon and the duration of action. If succinylcholine is used before Pavulon, the administration of Pavulon should be delayed until the succinylcholine shows signs of wearing off.

DOSAGE AND ADMINISTRATION: Pavulon should be administered only by or under the supervision of experienced clinicians. DOSAGE MUST BE INDIVIDUALIZED IN EACH CASE. See package insert for suggested dosages.

CAUTION: Federal law prohibits dispensing without prescription.

HOW SUPPLIED:

2 ml. ampuls—2 mg./ml.—boxes of 25, NDC # 0052-0444-26
5 ml. ampuls—2 mg./ml.—boxes of 25, NDC # 0052-0444-25
10 ml. vials—1 mg./ml.—boxes of 25, NDC # 0052-0443-25

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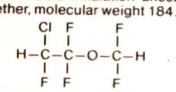
Please see complete use information on following page.

Ethrane® (enflurane)

CAUTION: Federal Law Prohibits Dispensing without Prescription.

DESCRIPTION

ETHRANE (enflurane) is a nonflammable inhalation anesthetic agent. It is 2-chloro-1, 1,2-trifluoroethyl difluoromethyl ether, molecular weight 184.5, and its structural formula is:



The boiling point is 56.5°C at 760 mm Hg. and the vapor pressure (mm Hg) is 175 at 20°C, 218 at 25°C, and 345 at 36°C. Vapor pressures can be calculated using the equation:

$\log_{10}P=A+B/T \quad A=7.967$

$B=-1678.4$

$T=°C+273.16$ (Kelvin)

The specific gravity (25°/25°C) is 1.517. The refractive index at 20° is 1.3026-1.3030. The blood/gas coefficient is 1.91 at 37°C and the oil/gas coefficient is 98.5 at 37°C. The M.A.C. (minimum alveolar concentration) in man is 1.68 percent in pure oxygen, 0.57 in 70% nitrous oxide and oxygen, and 1.17 in 30% nitrous oxide and oxygen.

ETHRANE is a clear, colorless, stable liquid whose purity exceeds 99.9 percent (area % by gas chromatography). No chemical stabilizers are added as these have been found, through controlled laboratory tests, to be unnecessary to maintain stability even in the presence of ultraviolet light. ETHRANE is stable to strong base and does not decompose in contact with soda lime and does not attack aluminum, tin, brass, iron or copper. The partition coefficients of ETHRANE at 25°C are 74 in conductive rubber and 120 in polyvinyl chloride.

CLINICAL PHARMACOLOGY

ETHRANE (enflurane) is an inhalation anesthetic. Induction and recovery from anesthesia with ETHRANE are rapid. ETHRANE has a mild, sweet odor. There is mild stimulus to salivation or tracheobronchial secretions when ETHRANE is used alone. Pharyngeal and laryngeal reflexes are readily obtunded. The level of anesthesia changes rapidly with ETHRANE. ETHRANE reduces ventilation as depth of anesthesia increases. High pCO_2 levels can be obtained at deeper levels of anesthesia if ventilation is not supported. ETHRANE provokes a sigh response reminiscent of that seen with diethyl ether.

There is a decrease in blood pressure with induction of anesthesia, followed by a return to near normal with surgical stimulation. Progressive increases in depth of anesthesia produce corresponding increases in hypotension. Heart rate remains relatively constant without significant bradycardia. Electrocardiographic monitoring or recordings indicate that cardiac rhythm remains stable. Elevation of the carbon dioxide level in arterial blood does not alter cardiac rhythm.

Studies in man indicate a considerable margin of safety in the administration of epinephrine containing solutions during ETHRANE anesthesia. ETHRANE anesthesia has been used in excision of pheochromocytoma in man without ventricular arrhythmias. On the basis of studies in patients anesthetized with ETHRANE and injected with epinephrine containing solutions to achieve hemostasis in a highly vascular area (transphenoidal surgery), it is recommended that 2 micrograms per kilogram (2 μg/kg) of epinephrine may be injected subcutaneously over a 10 minute period. This may be repeated up to 3 times per hour.

Example: Up to 10 ml of 1:100,000 epinephrine containing solution (10 μg/ml) may be injected subcutaneously over a 10 minute period in a 50 kilogram patient judged to have ordinary tolerance to epinephrine administration. No more than 30 ml of 1:100,000 epinephrine containing solution (10 μg/ml) should be administered to such a patient per hour. The concomitant administration of lidocaine enhances the safety of the use of epinephrine during ETHRANE anesthesia. This effect of lidocaine is dose related. All customary precautions in the use of vasoconstrictor substances should be observed.

Example Two: Alternatively, up to 20 ml of 1:200,000 epinephrine containing solution (5 μg/ml) may be substituted for 10 ml of 1:100,000 solution in the above example.

Muscle relaxation may be adequate for intra-abdominal operation at normal levels of anesthesia. Muscle relaxants may be used to achieve greater relaxation and all commonly used muscle relaxants are compatible with ETHRANE. The NONDEPOLARIZING MUSCLE RELAXANTS ARE POTENTIATED. In the normal 70 kg adult, 6 to 9 mg of d-tubocurarine or 1 to 1.5 mg of pancuronium will produce a 90 percent or greater depression of twitch height. Neostigmine does not reverse the direct effect of ETHRANE.

Biotransformation of ETHRANE in man results in low levels of serum fluoride ions averaging 15 μM/L. These levels are well below the 50 μM/L threshold level which can produce minimal renal damage in normal subjects; however, it is possible that these levels could result in damage in patients with severely impaired renal function or those undergoing renal transplantation. Depression of lymphocyte transformation does not follow prolonged ETHRANE anesthesia in man in the absence of surgery. Thus ETHRANE does not depress this aspect of the immune response.

INDICATIONS

ETHRANE (enflurane) may be used for induction and maintenance of general anesthesia. Adequate data have not been developed to establish its application in obstetrical anesthesia.

CONTRAINDICATIONS

Seizure disorders (see WARNINGS).

Known sensitivity to ETHRANE (enflurane) or other halogenated anesthetics.

WARNINGS

Increasing depth of anesthesia with ETHRANE (enflurane) may produce a change in the electroencephalogram characterized by high voltage, fast frequency, progressing through spike-dome complexes alternating with periods of electrical silence to frank seizure activity. The latter may or may not be associated with motor movement. Motor activity, when encountered, generally consists of twitching or "jerks" of various muscle groups; it is self-limiting and can be terminated by lowering the anesthetic concentration. This electroencephalographic pattern associated with deep anesthesia is exacerbated by low arterial carbon dioxide tension. A reduction in ventilation and anesthetic concentration usually suffices to eliminate seizure activity. Cerebral blood flow and metabolism studies in normal volunteers immediately following seizure activity show no evidence of cerebral hypoxia. Mental function testing does not reveal any impairment of performance following prolonged ETHRANE anesthesia associated with or not associated with seizure activity.

Since levels of anesthesia may be altered easily and rapidly, only calibrated vaporizers which measure output with reasonable accuracy should be used. Hypotension and respiratory exchange can serve as a guide to anesthesia depth. Deep levels of anesthesia may produce marked hypotension and respiratory depression.

The action of nondepolarizing relaxants is augmented by ETHRANE. Less than the usual amounts of these drugs should be used. If the usual amounts of nondepolarizing relaxants are given, the time for recovery from myoneural blockade will be longer in the presence of ETHRANE than for other commonly used anesthetics.

Usage in Pregnancy: Safety in pregnancy has not been established. Reproduction studies have been performed in rats and rabbits, and there is no evidence of harm to the animal fetus. The relevance of these studies to the human is not known. Since there is no adequate experience in pregnant women who have received the drug, safety in pregnancy has not been established.

PRECAUTIONS

Bromsulfalein (BSP) retention is mildly elevated postoperatively in some cases. This may relate to the effect of surgery since prolonged anesthesia (5 to 7 hours) in human volunteers does not result in BSP elevation. There is some elevation of glucose and white blood count intraoperatively. Glucose elevation should be considered in diabetic patients. ETHRANE (enflurane) should be used with caution in patients who by virtue of medical or drug history could be considered more susceptible to cortical stimulation produced by this drug. As with other general anesthetics and some muscle relaxants, hyperpyrexia has been observed with the use of ETHRANE.

ADVERSE REACTIONS

1. Motor activity examplified by movements of various muscle groups and/or seizures may be encountered with deep levels of ETHRANE (enflurane) anesthesia, or light levels with hypocapnia.
2. Hypotension and respiratory depression have been reported.
3. Arrhythmias, shivering, nausea, and vomiting have been reported.
4. Elevation of the white blood count has been observed.

DOSAGE AND ADMINISTRATION

The concentration of ETHRANE (enflurane) being delivered during anesthesia from a vaporizer should be known. This may be accomplished by using:

a) vaporizers calibrated specifically for ETHRANE.

b) vaporizers from which delivered flows can easily and readily be calculated.

Nothing is present in the agent to alter calibration or affect the operation characteristics of the vaporizer.

Preanesthetic Medication: Preanesthetic medication should be selected according to the need of the individual patient, taking into account that secretions are weakly stimulated by ETHRANE and the heart rate remains constant. the use of anticholinergic drugs is a matter of choice.

Induction: Induction may be achieved using ETHRANE alone with oxygen or in combination with oxygen-nitrous oxide mixtures. Under these conditions some excitement may be encountered. If excitement is to be avoided, a hypnotic dose of a short-acting barbiturate should be used to induce unconsciousness, followed by the ETHRANE mixture. In general, inspired concentrations of 2.0-4.5% ETHRANE produce surgical anesthesia in 7-10 minutes.

Maintenance: Surgical levels of anesthesia may be maintained with 0.5-3% ETHRANE. Maintenance concentrations should not exceed 3%. If added relaxation is required, supplemental doses of muscle relaxants may be used. Ventilation to maintain the tension of carbon dioxide in arterial blood in the 35-45 mm Hg range is preferred. Hyperventilation should be avoided in order to minimize possible CNS excitation.

The level of blood pressure during maintenance is an inverse function of ETHRANE concentration in the absence of other complication problems. Excessive decreases (unless related to hypovolemia) may be due to depth of anesthesia and in such instances should be corrected by lightening the level of anesthesia.

Overdosage: In the event of overdosage, or what may appear to be overdosage, the following action should be taken.

Stop drug administration; establish a clear airway and initiate assisted or controlled ventilation with pure oxygen.

PACKAGING

ETHRANE (enflurane) is packaged in 125 and 250 ml amber colored bottles.

Ohio Medical Anesthetics

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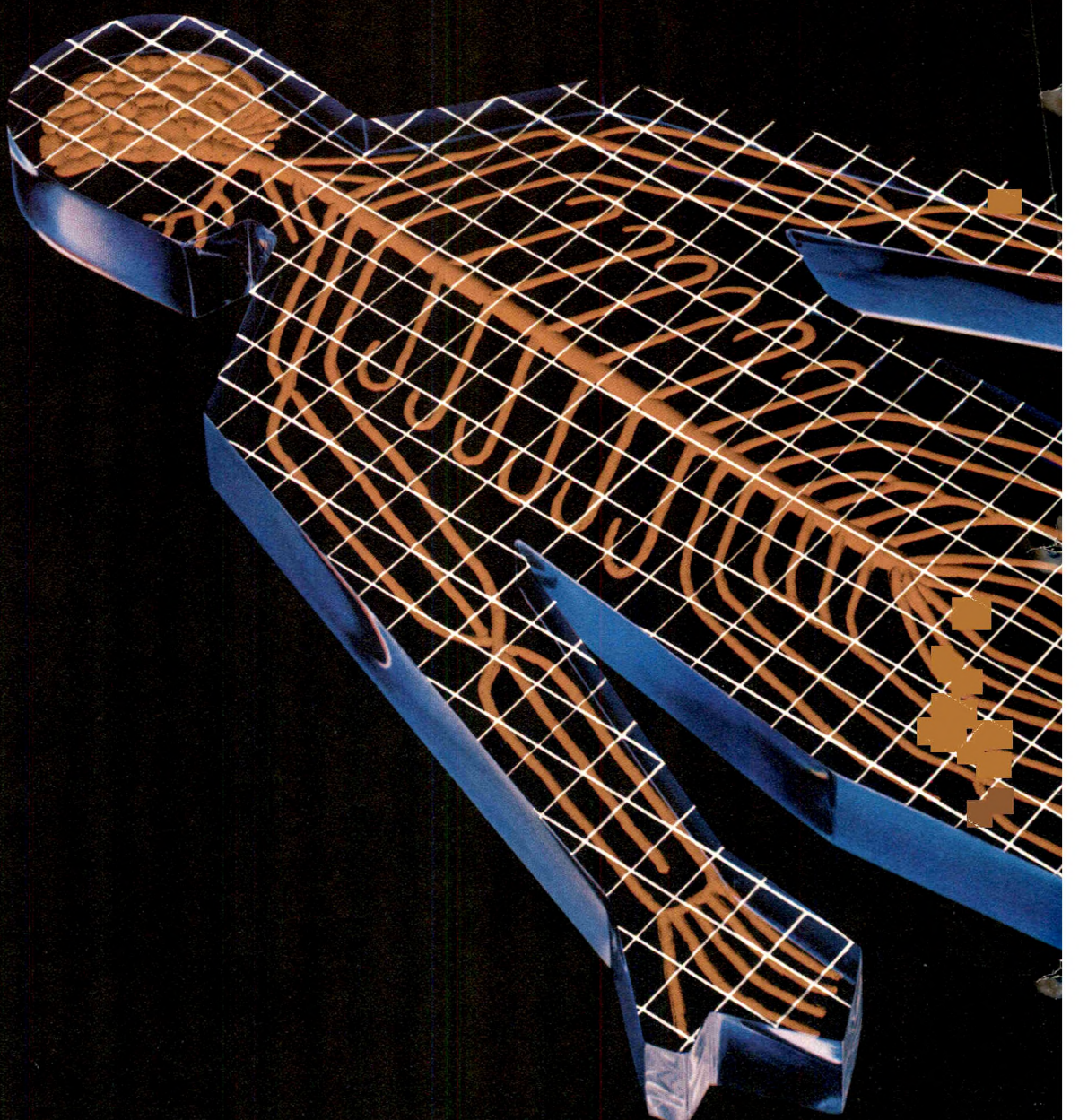
PHYSIO CONTROL

The VSM1 Vital Signs Monitor from Physio-Control.

Physio-Control Corporation · Cardiovascular Division · 11811 Willows Road · Redmond, Washington 98052 USA · (206) 881-4000

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An ideal choice for regional anesthesia

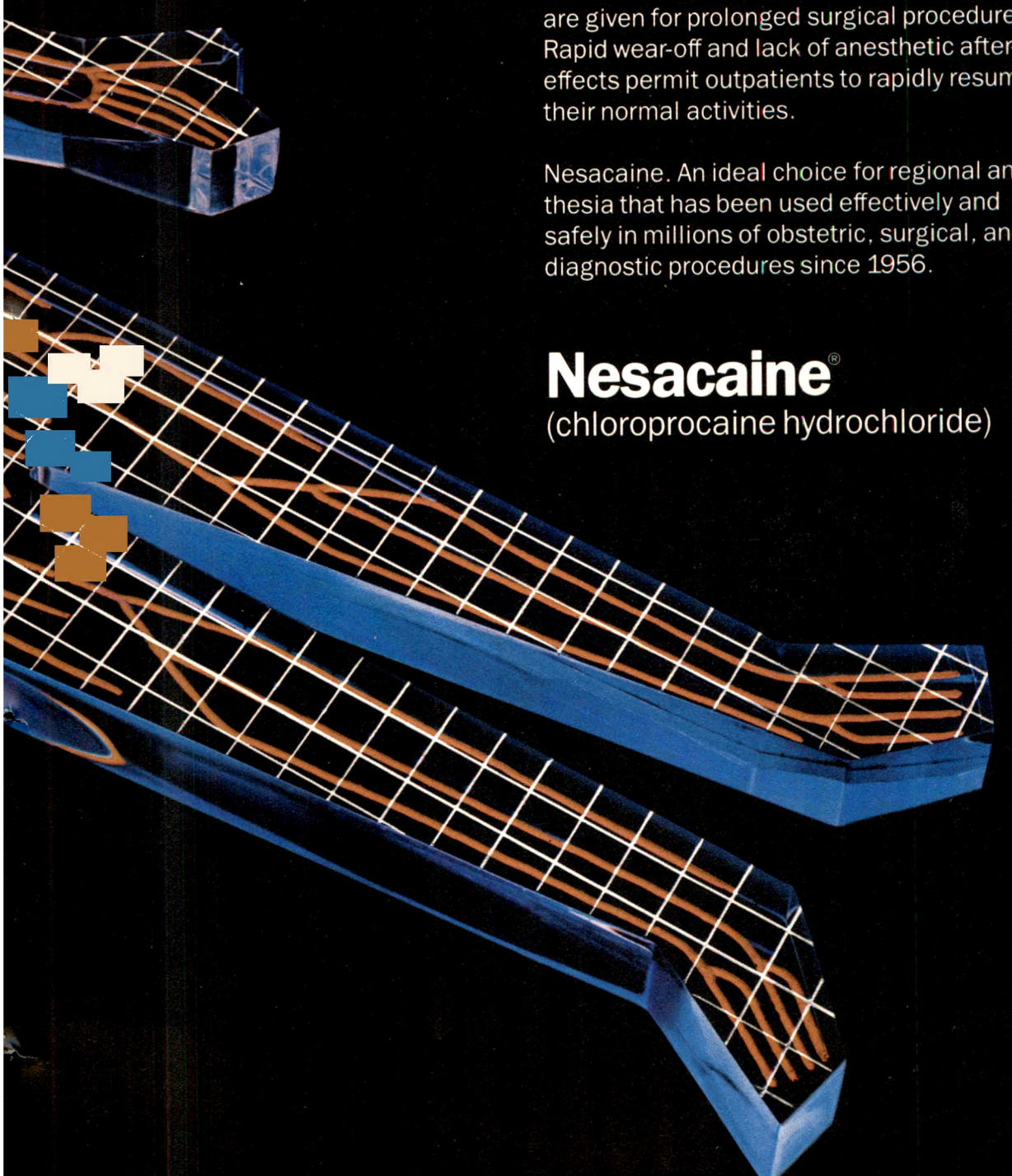


A-306 1-82

. . . for over 25 years

Nesacaine offers ideal advantages in regional anesthesia: rapid onset of action, rapid hydrolysis and rapid wear-off. Rapid onset allows rapid evaluation of the success of the nerve block and allays patient anxieties about anesthetic effectiveness. Rapid hydrolysis by plasma cholinesterase gives Nesacaine a built-in safety mechanism. It minimizes chances of systemic, CNS or cardiovascular side effects, even when additional injections are given for prolonged surgical procedures. Rapid wear-off and lack of anesthetic after-effects permit outpatients to rapidly resume their normal activities.

Nesacaine. An ideal choice for regional anesthesia that has been used effectively and safely in millions of obstetric, surgical, and diagnostic procedures since 1956.



Nesacaine®
(chloroprocaine hydrochloride)

Please turn page for brief summary of prescribing information.

Nesacaine®
(chloroprocaine hydrochloride)

Nesacaine®-CE
(chloroprocaine hydrochloride)

BRIEF SUMMARY:
Nesacaine, in multidose vials with preservative, is indicated for the production of local anesthesia by infiltration and regional nerve block; it should not be used for caudal or epidural anesthesia.

Nesacaine-CE, in single dose vials without preservative, is indicated for the production of local anesthesia by infiltration and regional nerve block, including caudal and epidural blocks.

Contraindications: hypersensitivity to drugs of the PABA ester group; central nervous system disease is a contraindication to caudal or epidural block.

Warnings: RESUSCITATIVE EQUIPMENT AND DRUGS SHOULD BE IMMEDIATELY AVAILABLE WHEN ANY LOCAL ANESTHETIC IS USED.

Usage in Pregnancy: Safe use of chloroprocaine HCl has not been established with respect to adverse effects upon fetal development. This fact should be carefully considered before administering the drug to women of childbearing potential, particularly during early pregnancy.

Obstetrical Paracervical Block: Chloroprocaine is not recommended for obstetrical paracervical block when toxemia of pregnancy is present or when fetal distress or prematurity is anticipated in advance of the block. Fetal bradycardia has been noted by electronic monitoring in about 5-10% of the cases where initial doses of 120 mg to 140 mg of chloroprocaine were used. The incidence of bradycardia, within this dose range, might not be dose related. These data are limited and are generally restricted to non-toxemic cases where fetal distress or prematurity was not anticipated in advance of the block. The role of drug factors and non-drug factors associated with fetal bradycardia following paracervical block are unexplained at this time.

In obstetrics, some oxytocic drugs may cause severe persistent hypertension if vasoconstrictor drugs are used to correct hypotension or are added to the local anesthetic solution.

Solutions containing vasoconstrictors, particularly epinephrine and norepinephrine, should be used with extreme caution in patients receiving MAO inhibitors and tricyclic antidepressants, since severe prolonged hypertension may occur.

Precautions: The safety and effectiveness of chloroprocaine HCl depends upon proper dosage, correct technique, adequate precautions and readiness for emergencies.

Solutions containing vasoconstrictors should be used cautiously in the presence of disease which may adversely affect the patient's cardiovascular system, in areas where the blood supply is limited, or when peripheral vascular disease is present.

Injections should always be made slowly and with frequent aspiration to avoid inadvertent rapid intravascular administration which can produce systemic toxicity.

Serious cardiac arrhythmias may occur if preparations containing a vasopressor are used in patients during or following the administration of chloroform, halothane, cyclopropane, trichlorethylene, or other related agents.

Adverse Reactions: *Systemic adverse reactions* result from high plasma levels due to rapid absorption, inadvertent intravascular injection, excessive dosage, hypersensitivity, idiosyncrasy, or diminished tolerance. *Central nervous system reactions:* excitation and/or depression; restlessness, anxiety, dizziness, blurred vision, or tremors, possibly proceeding to convulsions. Depression may be the first manifestation followed by drowsiness merging into unconsciousness and respiratory arrest.

Cardiovascular system reactions: depression of the myocardium manifested by an initial episode of hypotension, bradycardia, and cardiac arrest.

Neurologic adverse reactions: In the practice of epidural block, occasional inadvertent penetration of the subarachnoid space may occur; subsequent reactions may include spinal block of varying magnitude, loss of bowel and bladder control, loss of perineal sensation and sexual function. Persistent neurological deficit of some lower spinal segments with slow recovery (several months) has been reported in rare instances.

Dosage and Administration: See full prescribing information.

NESACAINE is supplied in 1% and 2% solutions in 30 ml multiple dose vials.

NESACAINE-CE is supplied in 2% and 3% solutions in 30 ml single dose vials.

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Only one premedicant does so many things so well



- **Provides prompt tranquilization**
- **Inhibits emesis during and after surgery**
- **Contributes to cardiovascular stability**

  Unique among premedicants, INAPSINE® (droperidol) provides vasodilation and mild alpha-adrenergic blocking effects which can help protect against undue hypertensive reactions and changes in heart rate.
  Troublesome hypotension is unlikely in the absence of hypovolemia. Has little or no adverse effect on the heart or circulation.
- **Reduces the need for postoperative narcotics**

A PROFILE OF CHARACTERISTICS UNMATCHED BY ANY OTHER SINGLE AGENT

	Inapsine® (droperidol) Injection	Diazepam Injection	Lorazepam Injection	Hydroxy-zine Injection
Class of tranquilizer	**Major**	Minor	Minor	Minor
Elimination half-life	**2.3 hrs.**	27-37 hrs.	16 hrs.	3-4 hrs.
Antiemetic activity	**Signifi-cant**	No	No	Mild
Alpha-adrenergic blockade	**YES**	No	No	No
May be used both IM and IV	**YES**	Yes (IM preferred)	Yes	No
Less pain on injection	**YES**	No	No	No
Same syringe compatibility with atropine, scopolamine	**YES**	No	No	Yes

Please see brief summary of Prescribing Information on next page.

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A premedicant that does more than premedicate

JANSSEN PHARMACEUTICA

Janssen Pharmaceutica Inc, 501 George St., New Brunswick, N.J. 08903

Inapsine®
(droperidol) Injection

Inapsine® (droperidol) Injection ℞

Before prescribing please consult complete prescribing information, of which the following is a brief summary.

DESCRIPTION:
2 ml. and 5 ml. ampoules
Each ml. contains:
Droperidol . . . . . 2.5 mg.
Lactic acid for pH adjustment to 3.4 ± 0.4
10 ml. vials
Each ml. contains:
Droperidol . . . . . 2.5 mg.
With 1.8 mg. methylparaben and 0.2 mg. propylparaben, and lactic acid for pH adjustment to 3.4 ± 0.4.
Protect from light. Store at room temperature.
FOR INTRAVENOUS OR INTRAMUSCULAR USE ONLY
Droperidol is a neuroleptic (tranquilizer) agent.

INDICATIONS: INAPSINE (droperidol) is indicated:
to produce tranquilization and to reduce the incidence of nausea and vomiting in surgical and diagnostic procedures;
for premedication, induction, and as an adjunct in the maintenance of general and regional anesthesia;
in neuroleptanalgesia in which INAPSINE (droperidol) is given concurrently with a narcotic analgesic, such as SUBLIMAZE® (fentanyl) injection, to aid in producing tranquility and decreasing anxiety and pain.

CONTRAINDICATIONS: INAPSINE (droperidol) is contraindicated in patients with known intolerance to the drug.

WARNINGS: FLUIDS AND OTHER COUNTERMEASURES TO MANAGE HYPOTENSION SHOULD BE READILY AVAILABLE. As with other CNS depressant drugs, patients who have received INAPSINE (droperidol) should have appropriate surveillance.
If INAPSINE (droperidol) is administered with a narcotic analgesic such as SUBLIMAZE (fentanyl), the user should familiarize himself with the special properties of each drug, particularly the widely differing durations of action. In addition, when such a combination is used, resuscitative equipment and a narcotic antagonist should be readily available to manage apnea. See package insert for fentanyl before using. Narcotic analgesics such as SUBLIMAZE (fentanyl) may cause muscle rigidity, particularly involving the muscles of respiration. This effect is related to the speed of injection. Its incidence can be reduced by the use of slow intravenous injection. Once this effect occurs, it is managed by the use of assisted or controlled respiration and, if necessary, by a neuromuscular blocking agent compatible with the patient's condition.
The respiratory depressant effect of narcotics persists longer than their measured analgesic effect. When used with INAPSINE (droperidol), the total dose of all narcotic analgesics administered should be considered by the practitioner before ordering narcotic analgesics during recovery from anesthesia. It is recommended that narcotics, when required, be used initially in reduced doses as low as ¼ to ⅓ those usually recommended.

PRECAUTIONS: The initial dose of INAPSINE (droperidol) should be appropriately reduced in elderly, debilitated and other poor-risk patients. The effect of the initial dose should be considered in determining incremental doses. Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics, can cause peripheral vasodilatation and hypotension because of sympathetic blockade. Through other mechanisms INAPSINE (droperidol) can also alter circulation. Therefore, when INAPSINE (droperidol) is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological alterations involved, and be prepared to manage them in the patients selected for this form of anesthesia.
If hypotension occurs, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should also be considered when operative conditions permit. It should be noted that in spinal and peridural anesthesia, tilting the patient into a head down position may result in a higher level of anesthesia than is desirable, as well as impair venous return to the heart. Care should be exercised in moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do not correct the hypotension, then the administration of pressor agents other than epinephrine should be considered. Epinephrine may paradoxically decrease the blood pressure in patients treated with INAPSINE (droperidol) due to the alpha-adrenergic blocking action of droperidol.
Since INAPSINE (droperidol) may decrease pulmonary arterial pressure, this fact should be considered by those who conduct diagnostic or surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient. Vital signs should be monitored routinely.
Other CNS depressant drugs (e.g. barbiturates, tranquilizers, narcotics, and general anesthetics) have additive or potentiating effects with INAPSINE (droperidol). When patients have received such drugs, the dose of INAPSINE (droperidol) required will be less than usual. Likewise, following the administration of INAPSINE (droperidol), the dose of other CNS depressant drugs should be reduced.
INAPSINE (droperidol) should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.
When the EEG is used for postoperative monitoring, it may be found that the EEG pattern returns to normal slowly.
Since INAPSINE (droperidol) is frequently used with the narcotic analgesic SUBLIMAZE (fentanyl), it should be noted that fentanyl may produce bradycardia, which may be treated with atropine; however, fentanyl should be used with caution in patients with cardiac bradyarrhythmias.*

ADVERSE REACTIONS: The most common adverse reactions reported to occur with INAPSINE (droperidol) are mild to moderate hypotension and occasionally tachycardia, but these effects usually subside without treatment. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. Postoperative drowsiness is also frequently reported.
Extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed following administration of INAPSINE (droperidol). Restlessness, hyperactivity, and anxiety which can be either the result of inadequate dosage of INAPSINE (droperidol) or a part of the symptom complex of akathisia may occur. When extrapyramidal symptoms occur, they can usually be controlled with anti-parkinson agents.
Other adverse reactions that have been reported are dizziness, chills and/or shivering, laryngospasm, bronchospasm and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression).
When INAPSINE (droperidol) is used with a narcotic analgesic such as SUBLIMAZE (fentanyl), respiratory depression, apnea, and muscular rigidity can occur; if these remain untreated respiratory arrest could occur. Elevated blood pressure, with or without preexisting hypertension, has been reported following administration of INAPSINE (droperidol) combined with SUBLIMAZE (fentanyl) or other parenteral analgesics. This might be due to unexplained alterations in sympathetic activity following large doses; however, it is also frequently attributed to anesthetic or surgical stimulation during light anesthesia.

DOSAGE AND ADMINISTRATION: Dosage should be individualized. Some of the factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used, and the surgical procedure involved. Vital signs should be monitored routinely.
Usual Adult Dosage

I. Premedication—(to be appropriately modified in the elderly, debilitated, and those who have received other depressant drugs) 2.5 to 10 mg. (1 to 4 ml.) may be administered intramuscularly 30 to 60 minutes preoperatively.

II. Adjunct to General Anesthesia
Induction—2.5 mg. (1 ml.) per 20 to 25 pounds may be administered (usually intravenously) along with an analgesic and/or general anesthetic. Smaller doses may be adequate. The total amount of INAPSINE (droperidol) administered should be titrated to obtain the desired effect based on the individual patient's response.
Maintenance—1.25 to 2.5 mg. (0.5 to 1 ml.) usually intravenously (see warning regarding use with concomitant narcotic analgesic medication and the possibility of widely differing durations of action).
If INNOVAR® injection is administered in addition to INAPSINE (droperidol), the calculation of the recommended dose of INAPSINE (droperidol) should include the droperidol contained in the INNOVAR injection. See INNOVAR injection Package Insert for full prescribing information.

III. Use Without A General Anesthetic In Diagnostic Procedures—Administer the usual I.M. premedication 2.5 to 10 mg. (1 to 4 ml.) 30 to 60 minutes before the procedure. Additional 1.25 to 2.5 mg. (0.5 to 1 ml.) amounts of INAPSINE (droperidol) may be administered, usually intravenously (see warning regarding use with concomitant narcotic analgesic medication and the possibility of widely differing durations of action).
Note: When INAPSINE (droperidol) is used in certain procedures, such as bronchoscopy, appropriate topical anesthesia is still necessary.

IV. Adjunct to Regional Anesthesia—2.5 to 5 mg. (1 to 2 ml.) may be administered intramuscularly or slowly intravenously when additional sedation is required.

HOW SUPPLIED: 2 ml. and 5 ml. ampoules-packages of 10; 10 ml. multiple-dose vials—packages of 10.
U.S. Patent No. 3,161,645
NDC 50458-010-02; NDC 50458-010-05; NDC 50458-010-10
March 1980, Revised June 1980
*See full prescribing information for complete description.

JANSSEN PHARMACEUTICA

Janssen Pharmaceutica Inc, 501 George St., New Brunswick, N.J. 08903

When it comes to infection control, this Ohio® mask has a clear advantage.



You probably already use a disposable circuit. Perhaps disposable filters and tracheal tubes, too. So why not complete your infection control program with the Ohio Disposable Anesthesia Breathing Mask.

Especially when the Ohio Disposable Mask helps you combat nosocomial infection. And contributes to your insight into your patient's status.

See-through patient monitoring.

The Ohio Disposable Mask is transparent. It maximizes visual access to your patient.

You instantly see expelled foreign matter in the mask. So you can take fast, corrective measures to prevent aspiration and assure airway patency.

By monitoring lip color and watching the formation of condensation on this transparent mask, you can get a better grasp of your patient's clinical status. You view clouding and clearing of the cone with each breath. And you study lip color to analyze both temperature and relative oxygen perfusion.

Single-use convenience.

Use the Ohio Disposable Mask once . . . and simply throw it away. Then, you don't have to worry about insufficient cleaning and sterilization. Or that the mask might pick up pathogens prior to use.

Gently conforms to your patient's face.

The Ohio Disposable Mask is available in three sizes to fit a wide variety of facial features.

The soft, malleable cushion holds its shape to help provide a tight seal and minimize facial marking. And the shape of the cone makes holding the mask easier, less tiresome for you.

Call your Ohio representative today. And find out how this new disposable mask makes a clear-cut contribution to your infection control program.

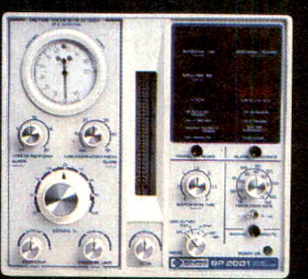
Ohio Medical Products

A Division of Airco, Inc.
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Bear Cub! It's your baby.

A new generation of infant ventilation. With built-in's, not add-on's.



We listen to you at Bear Medical Systems. Very carefully.

As a result, the things you said you wanted in an infant ventilator are in the all-new Bear Cub. Built in, not added on.

Just look at what comes with our new arrival:

Built-in, yet independent monitoring system digitally displays the actual ventilator rate, inspiratory and exhalation time, I:E ratio and mean airway pressure. This means quick, convenient set-up...and less chance of error at that critical time.

Integral alert and alarm package warns both audibly and visually of low inspiratory pressure, loss of PEEP/CPAP, prolonged inspiratory pressure, ventilator inoperative, and low air and oxygen pressures.

But monitoring and alarms/alerts aren't all we have added.

Higher 30 LPM flow rates extend the ventilator capabilities to include many pediatric patients.

Innovative servo-operated pneumatic control system provides greater variability of pressure waveforms and automatic inadvertent PEEP compensation.

Plus, such options as a 360 degree alarm light and a Fairfield mounting rail for accessories. And we promise superb service and support.

The new Bear Cub has all the convenience you have asked for in infant ventilation.

Congratulations...

It may be our ventilator, but it's your baby.

For full details, please contact us directly.





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Riverside, California 92503
Phone (714) 788-2460
TWX 910-332-6113

IN ANESTHESIOLOGY

STADOL®

(BUTORPHANOL TARTRATE)

...NOT JUST ANOTHER ANALGESIC



SAFETY IS THE DIFFERENCE

For an uneventful anesthesia course

In preop, you'll appreciate the good sedative effect of Stadol and reduction in patient apprehension.

Intraoperatively, Stadol provides smooth induction and emergence. The return to spontaneous respiration is rapid, so naloxone is rarely required.

In the recovery room, dosage can be repeated or increased, if necessary, to provide full pain relief with little fear of causing respiratory depression greater than that produced by 10 mg morphine.



Rebound respiratory depression, as sometimes seen in recovery after fentanyl, does not occur. Hypotensive effects are limited. Nausea or vomiting is rare.

Stadol is adaptable to a wide range of procedures, is compatible with your routines and is nonscheduled so you can keep it conveniently on your anesthesia cart.

Note: Stadol should not be administered to patients who have significant recent narcotic experience; its narcotic antagonist properties may induce withdrawal reactions unless detoxification is accomplished prior to use.

Stadol® IM IV

(butorphanol tartrate)

for moderate to severe pain…
the hospital-proven analgesic
with the safety difference

BRISTOL™

Bristol Laboratories
Division of Bristol-Myers Company
Syracuse, New York 13201

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Please see brief summary of prescribing information on adjoining page.

Stadol® IM IV
(butorphanol tartrate)

the effective analgesic with the safety difference

Brief Summary of Prescribing Information
STADOL® (butorphanol tartrate)

For complete information, consult Official Package Circular.

(2) 12/10/79

INDICATIONS AND USAGE—Stadol is recommended for the relief of moderate to severe pain. Stadol can also be used for preoperative or preanesthetic medication, as a supplement to balanced anesthesia, and for the relief of prepartum pain.

CONTRAINDICATIONS—Stadol should not be administered to patients who have been shown to be hypersensitive to it.

WARNINGS—Patients Physically Dependent on Narcotics: Because of its antagonist properties, Stadol is not recommended for patients physically dependent on narcotics. Detoxification in such patients is required prior to use.
Due to the difficulty in assessing addiction in patients who have recently received substantial amounts of narcotic medication, caution should be used in the administration of Stadol. Detoxification of such patients prior to usage should be carefully considered.

Drug Dependence: Special care should be exercised in administering Stadol to emotionally unstable patients and to those with a history of drug misuse. When long-term therapy is contemplated, such patients should be closely supervised. Even though Stadol has a low physical dependence liability, care should be taken that individuals who may be prone to drug abuse are closely supervised. It is important to avoid increases in dose and frequency of injections by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

Head Injury and Increased Intracranial Pressure: Although there is no clinical experience in patients with head injury, it can be assumed that Stadol, like other potent analgesics, elevates cerebrospinal fluid pressure. Therefore the use of Stadol in cases of head injury can produce effects (e.g., miosis) which may obscure the clinical course of patients with head injuries. In such patients Stadol must be used with extreme caution and only if its use is deemed essential.

Cardiovascular Effects: Because Stadol increases the work of the heart, especially the pulmonary circuit, the use of this drug in acute myocardial infarction or in cardiac patients with ventricular dysfunction or coronary insufficiency should be limited to those who are hypersensitive to morphine sulfate or meperidine.

PRECAUTIONS—Certain Respiratory Conditions: Because Stadol causes some respiratory depression, it should be administered only with caution and low dosage to patients with respiratory depression (e.g., from other medication, uremia, or severe infection), severely limited respiratory reserve, bronchial asthma, obstructive respiratory conditions, or cyanosis.

Impaired Renal or Hepatic Function: Although laboratory tests have not indicated that Stadol causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment. Extensive liver disease may predispose to greater side effects and greater activity from the usual clinical dose, possibly the result of decreased metabolism of the drug by the liver.

Biliary Surgery: Clinical studies have not been done to establish the safety of Stadol administration to patients about to undergo surgery of the biliary tract.

Usage as a Preoperative or Preanesthetic Medication: Slight increases in systolic blood pressure may occur, therefore caution should be employed when Stadol is used in the hypertensive patient.

Usage in Balanced Anesthesia: The use of pancuronium in combination with Stadol may cause an increase in conjunctival changes.

Usage in Pregnancy: The safety of Stadol for use in pregnancy prior to the labor period has not been established; therefore, this drug should be used in pregnant patients only when in the judgment of the physician its use is deemed essential to the welfare of the patient.

Reproduction studies have been performed in rats, mice and rabbits and have revealed no evidence of impaired fertility or harm to the fetus due to Stadol at about 2.5 to 5 times the human dose.

Usage in Labor and Delivery: Safety to the mother and fetus following administration of Stadol during labor has been established. Patients receiving Stadol during labor have experienced no adverse effects other than those observed with commonly used analgesics. Stadol should be used with caution in women delivering premature infants.

Usage in Nursing Mothers: The use of Stadol in lactating mothers who are nursing their infants is not recommended since it is not known whether this drug is excreted in human milk. Stadol has been used safely for labor pain in mothers who subsequently nursed their infants.

Usage in Children: Safety and efficacy in children below age 18 years have not been established.

ADVERSE REACTIONS—The most frequent adverse reactions in 1250 patients treated with Stadol are: sedation (503, 40%), nausea (82, 6%), clammy/sweating (76, 6%).
Less frequent reactions are: headache (35, 3%), vertigo (33, 3%), floating feeling (33, 3%), dizziness (23, 2%), lethargy (19, 2%), confusion (15, 1%), lightheadedness (12, 1%).
Other adverse reactions which may occur (reported incidence of less than 1%) are:

CNS: nervousness, unusual dreams, agitation, euphoria, hallucinations

Autonomic: flushing and warmth, dry mouth, sensitivity to cold

Cardiovascular: palpitation, increase or decrease of blood pressure

Gastrointestinal: vomiting

Respiratory: slowing of respiration, shallow breathing

Dermatological: rash or hives

Eye: diplopia or blurred vision

OVERDOSAGE—Manifestations: Although there have been no experiences of overdosage with Stadol during clinical trials, this may occur due to accidental or intentional misuse as well as therapeutic use. Based on the pharmacology of Stadol, overdosage could produce some degree of respiratory depression and variable cardiovascular and central nervous system effects.

Treatment: The immediate treatment of suspected Stadol overdosage is intravenous naloxone. The respiratory and cardiac status of the patient should be evaluated constantly and appropriate supportive measures instituted, such as oxygen, intravenous fluids, vasopressors and assisted or controlled respiration.

HOW SUPPLIED—Stadol (butorphanol tartrate) Injection for I.M. or I.V. use, is available as follows:

NDC 0015-5644-20—2 mg per ml, 2-ml vial
NDC 0015-5645-20—1 mg per ml, 1-ml vial
NDC 0015-5646-20—2 mg per ml, 1-ml vial
NDC 0015-5646-23—2 mg per ml, 1-ml Disposable Syringe
NDC 0015-5648-20—2 mg per ml, 10-ml multi-dose vial

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Cleveland, Ohio 44122

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The Ohio Haloscale MX Respirometer is the Wright's pattern anesthesia respirometer with *four* outlet connections.

Back, sides or top, you select the one outlet position that fits your machine and your technique best.

So no matter where you mount your Haloscale MX it's easy to read. And you don't have to worry about kinking tubes and occluding gas flow.

Unequalled accuracy.

Haloscale MX volume reports are meaningful because they're so accurate: ±2% at 16 LPM, +5 to +10% at 60 LPM. The reading range is broad, too—from 2.5 LPM to 300 LPM for any anesthesia procedure.

The versatile Haloscale MX can measure minute volume, tidal volume or vital capacity on its large, clear dial face. Dual scales let you track volume from 0 to 1 liter and 1 to 100 liters without clumsy conversion scales.

Controls are upfront.

Two touch-keyed control switches are mounted handily on the face of the Haloscale MX. ON/OFF freezes the dial at any point for quick recording in your patient's file. RESET not only returns the dial to zero but also works as an instant start system for quick volume measurements.

Service in the U.S.

Like all Ohio Haloscale Respirometers, the Haloscale MX can be serviced by our exclusive National Service Center. There's no longer a need to send a Haloscale abroad for a repair, no reason to risk accuracy at a local jeweler.

What's more, our Center will service your unit and have it back to you in ten working days or less—fully calibrated to factory specifications.

The Ohio Haloscale MX. From outlet options to U.S. service, it's the one respirometer that gives you all the right connections.

Ohio Medical Products

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WE CAN HELP YOU WITH YOUR BOARD EXAMINATIONS

Basic and Clinical Sciences in Anesthesiology

9th Edition 1980

by ARTHUR B. TARROW, MD, JEFFERSON MEDICAL COLLEGE
and JAMES C. ERICKSON, MD, NORTHWESTERN U. MEDICAL COLLEGE

This valuable study and review guide reflects the changing approach in both the written and oral examinations of the national examining bodies in Anesthesiology.

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PAEDIATRIC

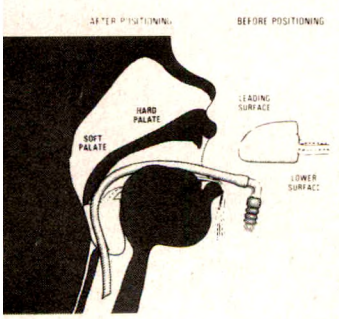
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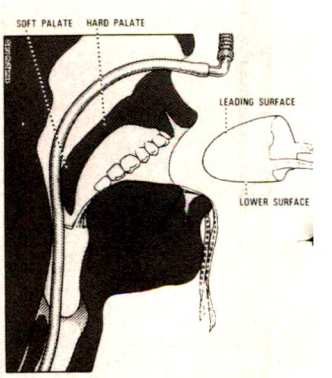
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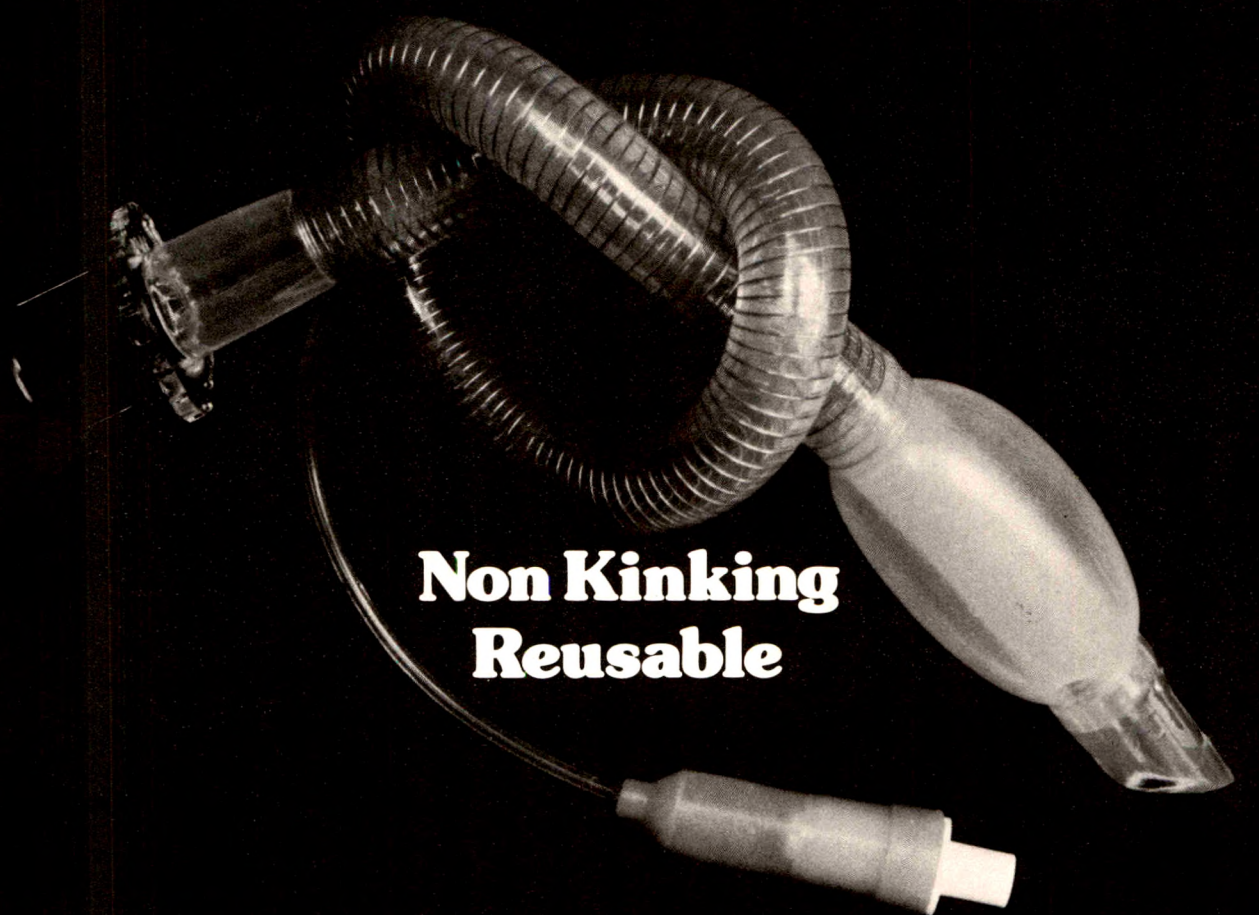
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Marcaine should be used cautiously in persons with known drug allergies or sensitivities, particularly to the amide-type local anesthetics.

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Excessive plasma levels of the amide-type local anesthetics cause systemic reactions involving the central nervous system and the cardiovascular system. The *central nervous system effects* are characterized by excitation or depression. The first manifestation may be nervousness, dizziness, blurred vision, or tremors, followed by drowsiness, convulsions, unconsciousness, and possibly respiratory arrest. Since excitement may be transient or absent, the first manifestation may be drowsiness, sometimes merging into unconsciousness and respiratory arrest. Other central nervous system effects may be nausea, vomiting, chills, constriction of the pupils, or tinnitus. The *cardiovascular manifestations* of excessive plasma levels may include depression of the myocardium, blood pressure changes (usually hypotension), and cardiac arrest. In obstetrics, cases of fetal bradycardia have occurred (see Warnings). *Allergic reactions*, which may be due to hypersensitivity, idiosyncrasy, or diminished tolerance, are characterized by cutaneous lesions (e.g., urticaria), edema, and other manifestations of allergy. Detection of sensitivity by skin testing is of doubtful value. Sensitivity to methylparaben preservatives added to multiple dose vials has been reported. Single dose vials without methylparaben are also available.

Reactions following epidural or caudal anesthesia also may include: high or total spinal block; urinary retention; fecal incontinence; loss of perineal sensation and sexual function; persistent analgesia, paresthesia, and paralysis of the lower extremities; headache and backache; and slowing of labor and increased incidence of forceps delivery.

Treatment of Reactions. Toxic effects of local anesthetics require symptomatic treatment; there is no specific cure. The physician should be prepared to maintain an airway and to support ventilation with oxygen and assisted or controlled respiration as required. Supportive treatment of the cardiovascular system includes intravenous fluids and, when appropriate, vasopressors (preferably those that stimulate the myocardium). Convulsions may be controlled with oxygen and intravenous administration, in small increments, of a barbiturate, as follows: preferably, an ultrashort-acting barbiturate such as thiopental or thiamylal; if this is not available, a short-acting barbiturate (e.g., secobarbital or pentobarbital) or diazepam. Intravenous barbiturates or anticonvulsant agents should only be administered by those familiar with their use.

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Marcaine 0.5% — Each ml contains 5 mg bupivacaine with NaCl for isotonicity in water for injection.

Marcaine 0.75% — Each ml contains 7.5 mg bupivacaine with NaCl for isotonicity in water for injection.

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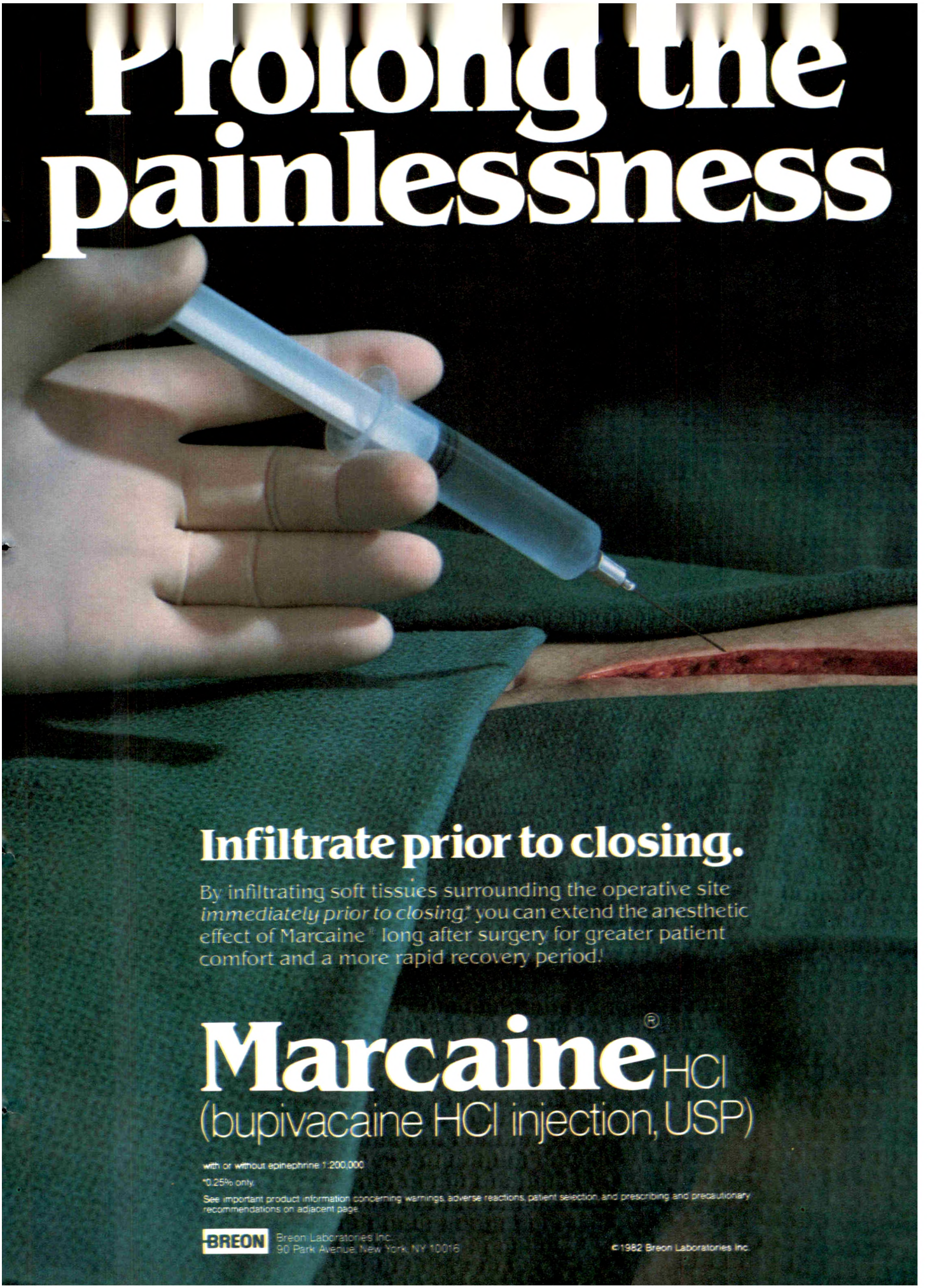
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Reference:

1. Buckley FP, Simpson BR: Acute traumatic and postoperative pain management. in Cousins MJ, Bridenbaugh PO (eds): *Neural Blockade in Clinical Anesthesia and Management of Pain*. Philadelphia, JB Lippincott Co., 1980 chap 25.

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ANESTH ANALG
1982;61:399-402

Lithium and Neuromuscular Transmission

B. E. Waud, MD, L. Farrell, BA, and D. R. Waud, MD, D Phil

WAUD, B. E., FARRELL, L., AND WAUD, D. R.: Lithium and neuromuscular transmission. Anesth Analg 1982;61:399–402.

The actions of lithium on end-plate depolarization and on indirect and direct twitch response of isolated guinea pig muscle were investigated. At clinical concentrations lithium did not cause depolarization, nor did it affect the depolarizing action of carbachol. Lithium also had no effect on the twitch response to nerve stimulation throughout its therapeutic serum concentration range and it did not alter the ED_{50} of pancuronium. When animals were chronically pretreated with lithium there appeared to be a slight reduction in dosage requirement for *d*-tubocurarine. At concentrations well above therapeutic serum levels, end-plate depolarization as well as indirect and direct twitch responses were depressed. It is concluded that, at therapeutic levels, there is minimal interaction of lithium with competitive neuromuscular blocking agents.

Key Words: PHARMACOLOGY: lithium; NEUROMUSCULAR TRANSMISSION: lithium; NEUROMUSCULAR RELAXANTS: *d*-tubocurarine, pancuronium.

LITHIUM shares many properties with sodium and potassium. Additionally, because of its smaller ionic radius, large sphere of hydration, and high charge density, lithium has been said functionally to resemble calcium and magnesium (1). It currently remains unknown whether these ionic characteristics have any relationship to lithium's therapeutic effects. The efficacy of lithium in the treatment of manic-depressive psychosis was first shown by Cade in 1949 (2). During recent years the use of lithium has increased and broadened to include other forms of mental disorders, and it is also used to reduce infection and leukopenia during systemic chemotherapy (3). Some reports (4–6) have suggested an interaction of lithium with neuromuscular blocking agents under clinical conditions. The following study was undertaken to evaluate quantitatively, and in a well controlled in vitro system, the cellular effects of lithium on neuromuscular transmission, in particular, whether lithium could, like calcium and potassium (7), alter the sensitivity of the neuromuscular junction to competitive neuromuscular blocking agents.

Supported by grant NS12255 from National Institute of Neurological and Communicative Disorders and Stroke.

Received from the Departments of Anaesthesia and Pharmacology, University of Massachusetts Medical School, Worcester, Massachusetts. Accepted for publication January 11, 1982.

Reprint requests to Dr. B. E. Waud, Department of Anaesthesia, University of Massachusetts Medical School, 55 Lake Avenue North, Worcester, MA 01605.

Methods

The experiments were carried out on isolated guinea pig lumbrical muscle or nerve-lumbrical preparations (8) incubated in Krebs solution of the following composition: sodium, 138 mM; potassium, 5.9 mM; calcium, 2.5 mM; magnesium, 1.22 mM; chloride, 123 mM; dihydrogen phosphate, 1.2 mM; sulfate, 1.22 mM; bicarbonate, 25 mM; plus glucose, 2.08 g/L. This solution was bubbled with 95% oxygen and 5% carbon dioxide and maintained at 37°C. The study consisted of two parts as follows.

Effect of Lithium on End-Plate Membrane

End-plate depolarization was recorded externally by Fatt's moving fluid electrode technique (9) [described in further detail by Waud and Waud (8)]. Lithium, in concentrations of 2, 10, 20, 40, or 100 mM was added to the muscle bath and depolarization measured at 5-minute intervals over 30 minutes. Additionally, three carbachol concentration-response curves were obtained. Graded concentrations of carbachol were added to the muscle bath and peak depolarizations were used to construct a control concentration-response curve. The concentration of lithium to be studied (2, 10, 20, or 40 mM) was then added to the bath and allowed to equilibrate for 30 minutes. The same doses of carbachol were repeated. Finally, a third curve was obtained after the lithium was washed out. Four to six muscles were studied at each concentration of lithium. Concentration-re-

sponse curves were fitted to these data as previously described [(8), equation 1 and figure 3] to obtain a quantitative estimate of the extent of depression of the depolarization response.

Effect of Lithium on Twitch Response

For indirect stimulation, the nerve was placed in a tunnel electrode and stimulated every 10 seconds with 0.3-msec pulses of twice maximal intensity. The resting muscle length was adjusted to give maximally developed tension. The preparation was equilibrated until twitch response was stable (approximately 30 minutes) and one of three drug regimens was then followed.

First, graded concentrations of lithium alone were added to the muscle bath to obtain a twitch height-versus-lithium concentration-response curve from which the lithium concentration that blocked the twitch height by 50% (ED_{50}) was then determined. (To obtain an objective estimate of these ED_{50} values, a sigmoid function, specifically twitch height = $1 - [drug]^P/([drug]^P + ED_{50}^P)$, where the parameter P determines the slope of the curve, was fitted to the observations by an iterative least-squares technique analogous to that used previously in this laboratory (8).

To assess how much of the depression of the indirectly elicited response was due to an action on muscle as opposed to one on neuromuscular transmission, the effect of lithium on the response of the muscle to direct stimulation was examined in parallel studies that were identical with the preceding series except that the muscles were stimulated directly (in the presence of 4 μM tubocurarine). The stimuli for direct stimulation were of supramaximal intensity, 0.5-msec duration delivered every 10 seconds. The polarity of the stimulating current was reversed automatically every other pulse to reduce artifacts due to polarization of electrodes and electrolysis.

Second, in order to increase the possibility of detecting a slight effect of lithium, the margin of safety of neuromuscular transmission was reduced by adding *d*-tubocurarine or pancuronium to the bath in a concentration that only slightly blocked the twitch height (no block to 10% block). After the muscle had been in the bath for ½ hour the relaxant was added and the twitch response was allowed to restabilize (approximately 30 minutes). Graded doses of lithium were then added along with the neuromuscular blocking agent to give a concentration-response curve and a lithium ED_{50} for comparison with control lithium ED_{50} values as determined above.

Third, a concentration of lithium (1, 2, or 10 mM) was added to the bath and the twitch height was allowed to reach a steady state (approximately 30 minutes). Graded doses of *d*-tubocurarine or pancuronium were then added in addition to the lithium to generate a concentration-response curve for the neuromuscular blocking agent and an ED_{50} value, as described above. These ED_{50} values were compared with control estimates determined in preparations without lithium.

Finally, the effect of chronic exposure to lithium was examined by putting guinea pigs on a diet containing lithium at a level of 0.25% (lithium carbonate) for 9 to 25 days. This regimen was selected to give a plasma lithium in the range encountered during lithium therapy in psychiatry. In the present experiments a mean level of 0.78 ± 0.22 (SD) mM was achieved.

It is often possible to get several muscles from one animal. Generally, when this was done the muscles from one animal were used in different assays so as not to reduce the error of estimate artificially. However, both because the variation among muscles in a given animal was of the same order of magnitude as that between animals and because we did not wish to kill any animals unnecessarily, occasionally we used two preparations from the same animal in an assay. Thus, in presentation of results (see Tables 1 and 2) we indicate both the number of preparations (muscles) and the number of animals.

Initially we tried to do several assays in a given muscle. However, this can be risky inasmuch as the longer the experiment the greater the likelihood that recovery to the initial state cannot be demonstrated on washout of drugs in which case the experiment must be discarded. Therefore, for most of the study we used a fresh muscle for each assay.

TABLE 1

Effect of Lithium on Twitch Response to Indirect and Direct Stimulation*

	Normal diet	Lithium diet
	mM	
Indirect stimulation	44.9 ± 4.4 (5, 5)	46.1 ± 5.7 (6, 5)
Direct stimulation	41.4 ± 2.3 (8, 6)	47.2 ± 4.5 (5, 4)
Indirect and tubocurarine†	38.1 ± 3.3 (6, 6)	
Indirect and pancuronium†	40.8 ± 4.2 (3, 3)	

* Values are lithium concentrations (±SE) reducing twitch response to 50% of control. Number of preparations and animals are shown in parentheses.

† Neuromuscular blocking agent was present in concentration producing minimal level of neuromuscular block (see "Methods").

TABLE 2

Effect of Lithium on ED_{50} of *d*-Tubocurarine and Pancuronium*

	Normal diet	Lithium diet
	μM	
d-Tubocurarine		
Control	0.585 ± 0.023 (4, 3)	0.440 ± 0.037 (6, 6)
Lithium (1 mM)	0.619 ± 0.051 (4, 3)	
Lithium (2 mM)	0.548 ± 0.038 (4, 4)	0.399 ± 0.036 (5, 5)
Lithium (10 mM)	0.491 ± 0.016 (5, 4)	
Pancuronium		
Control	0.122 ± 0.007 (9, 6)	0.118 ± 0.012 (5, 5)
Lithium (2 mM)	0.116 ± 0.009 (4, 3)	0.115 ± 0.011 (5, 5)
Lithium (10 mM)	0.134 ± 0.010 (5, 4)	

* Values are concentration (±SE) of *d*-tubocurarine or pancuronium reducing twitch response to nerve stimulation to 50% of control. Number of preparations and animals are shown in parentheses.

Results

Effect of Lithium on End-Plate Membrane

Lithium alone, regardless of concentration used (1 to 100 mM) failed to depolarize the end-plate region. Furthermore, concentrations of lithium used clinically (0.6 to 1.6 mM) (10) failed to shift the carbachol concentration-response curve. However, concentrations of 10 mM and greater reversibly shifted the carbachol curve downward. The magnitude of depression of carbachol-induced depolarization increased with increasing concentrations of lithium (see Fig 1).

Effect of Lithium on Indirect and Direct Twitch Responses

The concentration of lithium alone required to produce 50% block in twitch height was 44.9 ± 4.4 mM. This is approximately 40 times the therapeutic serum levels used clinically. Furthermore, the direct response was blocked by a concentration (41.4 ± 2.3 mM) indistinguishable from that affecting the indirect response (Table 1, Fig 2). Preparations from animals that were chronically exposed to lithium behaved similarly to those that were only acutely exposed to lithium (Table 1, right column). Reducing the margin of safety with either *d*-tubocurarine or pancuronium still gave a similar sensitivity to lithium (Table 1, last two rows).

Effect of Lithium on Sensitivity to Competitive Neuromuscular Blocking Agents

In Table 2 is shown that generally in the acute experiments, the ED_{50} values for both tubocurarine and pancuronium were unaffected by concomitant exposure of the nerve-muscle preparation to 1, 2, or 10 mM lithium with the possible exception that, in the presence of 10 mM lithium, the ED_{50} for *d*-tubocurarine was reduced from 0.585 to 0.491 mM, a change significant at the 95% probability level. The effect of chronic exposure to the lithium appeared to depend on the drug examined. With *d*-tubocurarine, the ED_{50} was lower after chronic lithium pretreatment whereas the ED_{50} of pancuronium was unchanged. As with acute exposure there was no effect of 2 mM lithium on the ED_{50} of either drug.

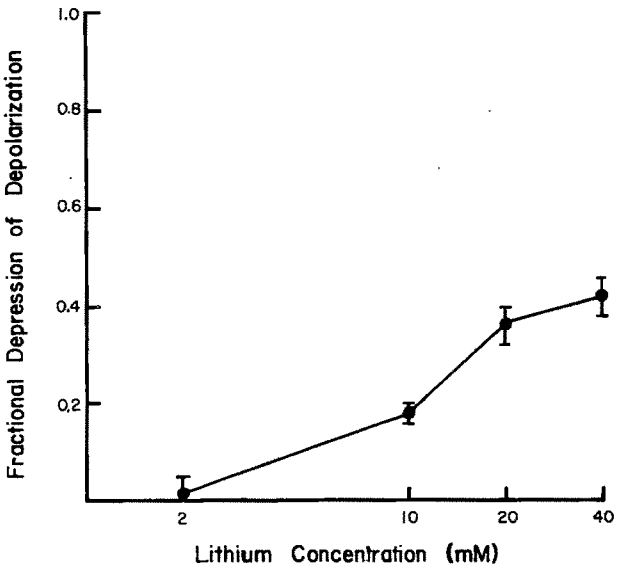


FIG 1. Dose-response curve for effect of lithium on carbachol-induced depolarization. Values are means ± SE (four to six preparations from three or four animals).

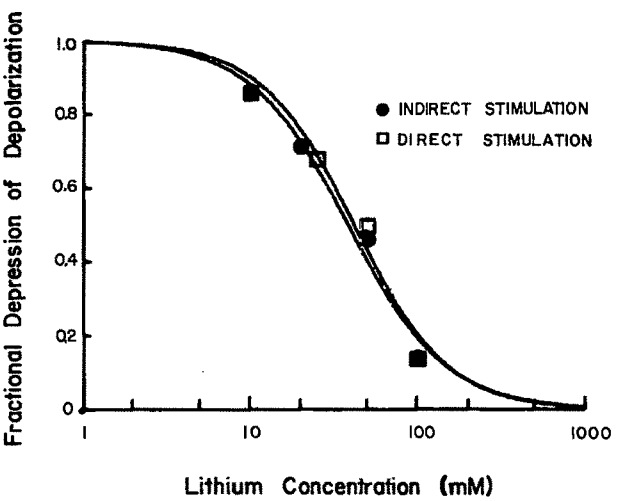


FIG 2. Experiment illustrating effect of lithium on directly and indirectly elicited twitch response. Curves represent least squares fit of logistic function (8). (Direct curve lies to left).

Discussion

Although previous reports suggest the potentiation of neuromuscular blockade by lithium under clinical conditions, the present study provides no strong evidence for a cellular basis for this effect. At concentrations to be expected clinically [i.e., 0.6 to 1.6 mM (10)], lithium had negligible effect on the membrane electrical behavior, on the response to carbachol, on the directly or indirectly elicited twitch, or on the sensitivity of the preparation to *d*-tubocurarine or pancuronium. Although effects could be found at high lithium concentrations, these would appear to be irrelevant to clinical use. They also appear to be relatively nonspecific as the directly elicited twitch is reduced to the same extent as the indirectly elicited response.

In Table 2 there were two "statistically significant" differences that deserve comment. First, the highest dose of lithium (10 mM) produced a slight reduction in the ED_{50} to *d*-tubocurarine but not to pancuronium. In fact, if anything, the ED_{50} of the latter increased. The easiest explanation is simply that one is dealing here with multiple *t*-tests; thus if one tests repeatedly at the 95% probability level there is a much greater than 5% chance that a spurious positive will appear. The other difference is more puzzling in that the animals on a chronic lithium diet showed a lower ED_{50} for *d*-tubocurarine both in the controls and at the level of 2 mM lithium. But this effect was not seen with pancuronium. The reason for this pattern is not clear.

It is difficult to explain with certainty why others have reported an in vivo effect of lithium. The most obvious explanations involve the less rigorous experimental control that is possible in an in vivo situation. Thus, the effect of lithium on the response to tubocurarine and pancuronium reported by Hill et al (6) might reflect a circulatory effect (the fact that "cardiovascular variables remained stable during these studies" does not rule out a change in distribution to muscle, whereas the reported change in kinetics of onset argues strongly for it) or random drift of the preparation (the authors did not bracket their lithium responses between two controls to close this loophole). In the case report of Borden et al (4) not even a record of the response to nerve stimulation is available so even the magnitude of the phenomenon observed is ill defined. Also the strong probability exists that the observed prolonged action of pancuronium had nothing to do with lithium.

Thus, putting all the available information together leads to the conclusion that, as used clinically, lithium is unlikely to have a direct effect on neuromuscular transmission. In turn, the anesthesiologist faced with a patient receiving lithium has little reason to consider such a patient abnormal with regard to dose requirement for tubocurarine or pancuronium. Even if the effect of chronic lithium exposure on the response to *d*-tubocurarine is real, the effect is only a 25% reduction in dosage requirement, a change less than patient-to-patient variation and therefore one that would easily be accommodated by routine titration of the dosage of the neuromuscular blocking drug.

Finally, we may note parenthetically that the results are directly relevant only to competitive neuromuscular blocking agents. We did not examine depolarizing agents directly as the only suitable isolated organ preparations available involve muscles from amphibia or rodents and quantitative extrapolation of depolarization effects from these species to man is hazardous at best. In fact, direct measurement of succinylcholine effects would add little weight to the observation that lithium did not affect the action of carbachol on depolarization. This situation is in marked contrast to the case with competitive blocking agents in which effects in man are in excellent agreement with what has been found in other experimental systems (the authors are unaware of a single solidly documented exception to this statement). Thus, the best that can be said at present is that it appears unlikely that lithium would interact significantly with succinylcholine under clinical conditions.

REFERENCES

1. Haudala HS, Borison RL, Diamond BI. Potential hazards and application of lithium in anesthesiology. Anesthesiology 1979;50:534–7.
2. Cade JFJ. Lithium salts in the treatment of psychotic excitement. Med J Aust 1949;2:349–52.
3. Lyman GH, Williams CC, Preston D. The use of lithium carbonate to reduce infection and leukopenia during systemic chemotherapy. N Engl J Med 1980;302:257–60.
4. Borden H, Clarke M, Katz H. Use of pancuronium bromide in patients receiving lithium carbonate. Can Anaesth Soc J 1974;21:79–82.
5. Hill GE, Wong KC, Hodges MR. Potentiation of succinylcholine neuromuscular blockade by lithium carbonate. Anesthesiology 1976;44:439–42.
6. Hill GE, Wong KC, Hodges MR. Lithium carbonate and neuromuscular blocking agents. Anesthesiology 1977:46:122–6.
7. Waud BE, Waud DR. Interaction of calcium and potassium with neuromuscular blocking agents. Br J Anaesth 1980;52:863–6.
8. Waud BE, Waud DR. Comparison of effects of general anesthestics on end-plate of skeletal muscle. Anesthesiology 1975;43:540–7.
9. Fatt P. The electromotive action of acetylcholine at the motor end-plate. J Physiol 1950;111:408–22.
10. Noyes R. Lithium carbonate: a review. Dis Nerv Syst 1969;30:318–30.

ANESTH ANALG
1982;61:403-9

Effect of Halothane on Rested-State and Potentiated-State Contractions in Rabbit Papillary Muscle: Relationship to Negative Inotropic Action

Hirochika Komai, PhD,* and Ben F. Rusy, MD†

KOMAI, H., AND RUSY, B. F.: Effect of halothane on rested-state and potentiated-state contractions in rabbit papillary muscle: relationship to negative inotropic action. Anesth Analg 1982;61:403–9.

The effect of halothane on the availability of different sources of activator calcium for myocardial contraction was evaluated in relationship to the negative inotropic effect of the anesthetic. This was studied in rabbit papillary muscle under various stimulation conditions that are known to vary the importance of one or another of two sources of Ca^{2+} for production of contraction. The rested-state contraction is known to depend primarily on the transsarcolemmal influx of Ca^{2+} for its activation whereas the potentiated-state contraction is dependent largely on Ca^{2+} released from intracellular stores. In the presence of 0.6% halothane (gas phase) the rested-state and potentiated-state contractions were depressed (mean ± SEM) 38% ± 5% (n = 15) and 32% ± 3% (n = 7), respectively (no statistically significant difference). Halothane accelerated the decay of the potentiated state, indicating that it stimulates the loss of Ca^{2+} from internal stores. Halothane also acted to slow the time course of force increase following restimulation of rested muscles, indicating that it inhibits the filling of internal stores. These observations suggest that the negative inotropic effect of halothane is caused by a combination of quantitatively similar effects of the anesthetic on the transsarcolemmal and intracellular sources of activator Ca^{2+}.

Key Words: ANESTHETICS, Volatile: halothane; HEART: contractility.

IT IS KNOWN that halothane, under appropriate in vitro experimental conditions, affects virtually all of the processes implicated in the cardiac excitation-contraction mechanism. Electrophysiologic studies indicate that halothane shortens the action potential duration in sheep ventricular muscle (1) and depresses the magnitude of slow action potential in guinea pig papillary muscle (2). Measurements of La^{3+}-displaceable Ca^{2+} in dog trabecular muscle indicate that halothane reduces the amount of superficially bound Ca^{2+} (3). Caffeine contracture studies with skinned muscle of rabbit indicate that halothane inhibits Ca^{2+} uptake by sarcoplasmic reticulum (4), although recently it has been reported (5) that this action may depend on abnormal environmental conditions. The results of experiments from this laboratory on the effect of halothane on the decay of potentiated state in cat papillary muscle indicate that the anesthetic most likely accelerates the loss of stored Ca^{2+} during diastole (6). Although each of these experimental methods may be suitable for studying the effect of halothane on a particular cardiac cellular organelle or process, effects on other associated processes are rarely elucidated. Consequently, it has not been possible to evaluate the significance or importance of the effect of halothane on a particular process in relationship to other processes that contribute to the negative inotropic effect of the anesthetic on intact myocardium. In the present study we have attempted to evaluate the relative contributions of effects of halothane on several different processes involved in myocardial excitation-contraction coupling. We have studied these effects by examining the action of halothane on force development in intact rabbit papillary muscles under conditions of varying stimulation frequency. The rationale for such experiments is that in a potentiated state produced, for example, by paired pulse stimulation or by high stimulation frequencies, the magnitude of developed force is largely deter-

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Supported in part by the Research and Development Fund of the Department of Anesthesiology, University of Wisconsin.

Received from the Department of Anesthesiology, Center for Health Sciences, University of Wisconsin, Madison, Wisconsin 53792. Accepted for publication January 18, 1982. Presented in part at the Annual Meeting of the American Society of Anesthesiologists, October 21, 1981, New Orleans, Louisiana.

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mined by the amount of internally stored Ca^{2+}, whereas at low stimulation frequencies, especially in the rested state, the magnitude of the developed force is largely determined by the amount of Ca^{2+} that enters the myocardium transarcolemmally during the action potential (7, 8). Although the effects of halothane on the developed force of rested-state condition in cat atrial muscle (9) and of potentiated-state condition in cat papillary muscle (10) and in rat muscle (11) have been reported, it has not been possible to compare the relative importance of these two effects as they have been examined in different species and under different environmental conditions. In the present work we compared the effect of halothane on myocardial performance under the contractile states specified above in a single model, the isolated but intact, rabbit papillary muscle.

Methods and Materials

Rabbits (mean weight 2.1 ± 0.2 (SD) kg, n = 32) were anesthetized by intravenous injection of pentobarbial (approximately 45 mg/kg). The heart was excised, and one papillary muscle from the right ventricle was isolated from each heart. The muscle was mounted vertically in a tissue bath (45 ml) maintained at 30°C. The lower end of the muscle was tied to a fixed base and the upper end to a stainless steel wire attached to a Statham UC-2 force transducer. Developed force was recorded on a Gilson polygraph. The length and cross-sectional areas of the muscle were obtained from measurements of muscle length and diameter by an ocular micrometer using a Unitron binocular microscope. Dimensions (mean ± SD) of the 32 muscles used in this study were, length 4.5 ± 1.4 mm; cross-sectional area, 0.55 ± 0.23 mm^2. The force was expressed in units of grams per square millimeter (force equivalent to 1 g of mass in the gravitational field per cross-sectional area of muscle in square millimeters). The muscle was stimulated at 0.1 Hz for 2 to 3 hours to allow stabilization of the preparation. The stimuli (4 msec duration, 1.5 × threshold) were delivered through silver-silver chloride field electrodes. A laboratory stimulator (American Electronics Laboratory) was used. The resting tension was maintained at 1 g in all the experiments.

The superfusing medium was a modified Krebs-Henseleit bicarbonate of the following composition; NaCl, 115 mM; KCl, 5.9 mM; $MgCl_2$, 1.2 mM; NaH_2PO_4, 1.2 mM; Na_2SO_4, 1.2 mM; $NaHCO_3$, 25 mM; $CaCl_2$, 2.5 mM; ethylenediaminetetraacetate (EDTA), 50 μM; and glucose, 5.6 mM. The medium was equilibrated with a gas mixture of 95% O_2 and 5% CO_2 by continuous bubbling. When the effect of halothane was studied, the anesthetic was added to the above gas mixture by a Fluotec vaporizer. The vaporizer was calibrated by gas chromatography using a Perkin-Elmer 910 gas chromatograph. Standard gas (Scottyl analyzed gas, 1.02% halothane) was supplied by Scott Specialty Gases. Twenty minutes of equilibration time was allowed after changing the composition of the gas. It was determined in separate experiments that the force of contraction of rabbit papillary muscles, paced at a frequency of 0.1 Hz, decreased with a half-life of approximately 4 minutes following a step increase (0 to 0.6%, 0 to 1.0%, or 0.6% to 1.0%) of halothane in the gas mixture. The 20-minute equilibration period that we used represents, therefore, approximately five half-lives, enough time for virtually complete equilibration. The tissue bath was partially closed to allow the escape of the gas to the atmosphere, whereas the gas phase in contact with the liquid medium was kept identical with that of the equilibrating gas. Rested state contraction was measured by stimulating the muscle after a period of 20 minutes without stimulation (8). Prior to the rest period the muscle was allowed to reach steady state at a sufficiently low stimulation frequency (0.1 Hz) to ensure that a true rested state was obtained. Potentiated state was generated by continuous paired-pulse stimulation. The intrapair interval was 300 msec. The effect of increasing stimulation frequency on the force of contraction was studied by restimulating briefly rested muscles at 2.0 Hz. This frequency was chosen because stable, close to maximum force of contraction was obtained at this frequency. Only the positive inotropic effect was analyzed, and the negative inotropic effect of activation (12) was not evaluated in this study. The time course of the biphasic change in developed force was analyzed by a graphic method in which a plot of the logarithm of the change in developed force against time was resolved into two exponential functions (13). Effect of halothane on the decay of potentiated state was also characterized by overall half-life (time for 50% decay) in addition to parameters in resolved exponential functions. The muscle preparations were found to be stable throughout the duration of experiments which usually lasted approximately 4 hours. The results were statistically evaluated by Student's paired or unpaired *t*-test as indicated.

Results

The effect of halothane on the developed force of rested-state contractions is shown in Table 1. The force of the rested-state contraction in the presence

TABLE 1
Effect of Halothane on Rested-State Contraction*

Halothane concentration	Developed force	Relative force†
%	g/mm^2	%
0 (n = 15)	0.41 ± 0.05	100
0.6 (n = 15)	0.26 ± 0.04‡§	62 ± 5
1.0 (n = 15)	0.18 ± 0.03‖§	42 ± 4

* Values are means ± SEM.
† Obtained from percentage of force for each muscle.
‡ $p < 0.05$, compared with control values (unpaired *t*-test).
§ $p < 0.01$, compared with control values (paired *t*-test).
‖ $p < 0.01$, compared with control values (unpaired *t*-test).

of 0.6% and 1.0% halothane corresponds respectively to 62% ± 5% and 42% ± 4% of the value in the absence of the anesthetic.

During paired-pulse stimulation in the absence of halothane, a maximal developed force was reached at a pair repetition frequency of 0.6 Hz. Increasing the stimulation frequency to 0.8 Hz or higher often resulted either in unstable force, which declined after reaching a maximum, or in failure of the second of the pair of pulses to potentiate the muscle. For this reason, the developed force obtained at 0.6 Hz in the absence of halothane was taken as the maximum potentiated-state developed forces for each muscle, and all the other developed forces for that muscle were expressed as a percentage of this value. With seven muscles, the developed force (mean ± SEM) of the maximally potentiated state in the absence of halothane was 3.35 ± 0.56 g/mm^2. Although the presence of halothane allowed paired-pulse stimulation of the muscle at a higher pair repetition frequency than in the absence of the anesthetic, increasing the frequency of paired-pulse stimulation did not overcome the negative inotropic effect of halothane. As can be seen in Fig 1, the maximum force in the presence of 0.6% and 1.0% halothane was 68% ± 3% and 38% ± 4% of that measured in the absence of the anesthetic. There was no statistically significant difference between the extent of halothane inhibition of potentiated-state contraction and that of rested-state contraction (see above) at either level of the anesthetic.

To evaluate the effect of halothane on the process of the decay of the potentiated state, we used paired-pulse stimulation frequencies of 0.6, 0.8, and 1.0 Hz in the presence of 0, 0.6%, and 1.0% halothane, respectively, to obtain maximally potentiated state based on the results of Fig 1. The developed force approaches the rested state as the length of time between the last of a train of potentiating paired pulses and a single test pulse is increased (loss of memory for the potentiated state). A plot of the

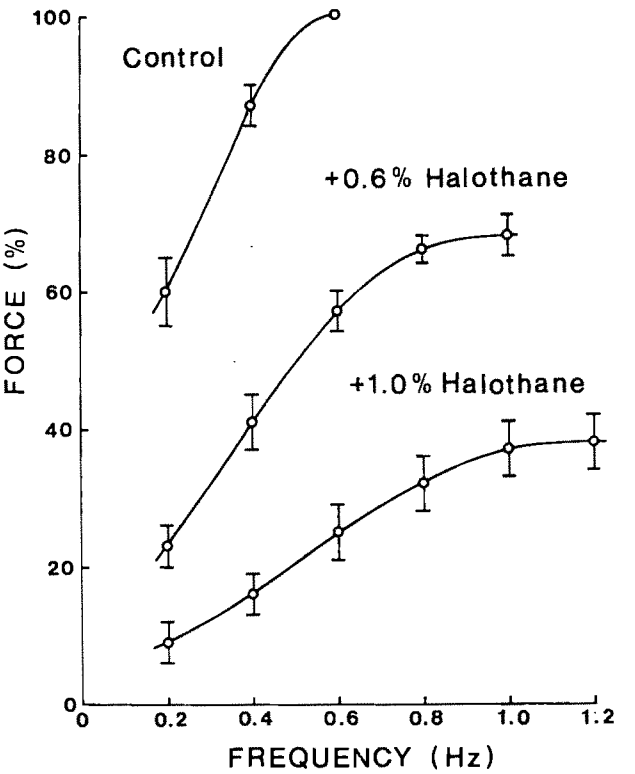


FIG 1. Effect of halothane on potentiated-state contraction at different pair repetition frequencies. Mean values (±SEM) of developed force expressed as percentages of control values were plotted against pair repetition frequency. For each muscle, force of contraction obtained at 0.6 Hz in absence of halothane was taken as 100%. Under optimal conditions (1.0 and 1.2 Hz in presence of 0.6% and 1.0% halothane, respectively), the extent of inhibition (mean ± SEM) was 32% ± 3% with +0.6% halothane and 62% ± 4% with +1.0% halothane.

logarithm of the difference between developed force (DF_t) of the single beat elicited by the test stimulus at time t after the last of the train of paired potentiating pulses and the developed force of the rested state ($DF_{rested\ state}$) versus time yielded a biphasic curve. As reported by Edman and Jóhannsson (14), an equation that describes the curve takes the form of:

$$DF_t - DF_{rested\ state} = \underbrace{Ae^{-k_1 t}}_{\text{(fast phase)}} + \underbrace{Be^{-k_2 t}}_{\text{(slow phase)}}$$

in which A and B are constants representing the maximum value (at t = 0) of the force assigned to the fast and slow phases and k_1 and k_2 are first-order rate constants. As can be seen in Fig 2 and Table 2, in rabbit papillary muscle, halothane reduced the magnitude of the slow, major component of the potentiated state (constant B) and shortened the overall half-life for the decay of the potentiated state, with little effect on constant A and on individual rate constants, k_1 and k_2.

When muscles were stimulated at 2.0 Hz after a brief (1 min) rest, the developed force increased to reach a steady-state value as shown in Fig 3, top. The time course of the increase in developed force was biphasic in the majority of muscles, but without the slow phase in some. A plot of the logarithm of the difference (ΔDF) between the developed force of the final steady state ($DF_{steady\ state}$) and the force at time t after the beginning of stimulation (DF) versus time yielded either a straight line or, more frequently, a

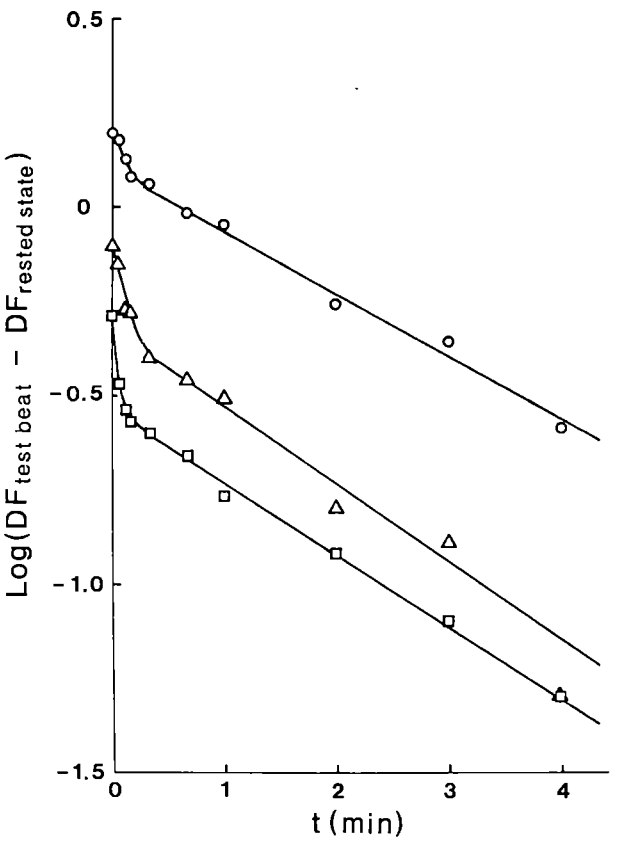


FIG 2. Effect of halothane on decay of potentiated state on control (○), +0.6% halothane (△), and +1.0% halothane (□). For this particular muscle preparation: control, DF = 0.29 + $0.34e^{-0.16t}$ + $1.26e^{-0.0063t}$; +0.6% halothane, DF = 0.12 + $0.32e^{-0.14t}$ + $0.47e^{-0.0076t}$; +1.0% halothane, DF = 0.08 + $0.23e^{-0.35t}$ + $0.28e^{-0.0073t}$, where DF is expressed in grams per square millimeter and t is expressed in seconds. Overall half-life: control, 72 seconds; +0.6% halothane, 22 seconds; +1.0% halothane, 14 seconds.

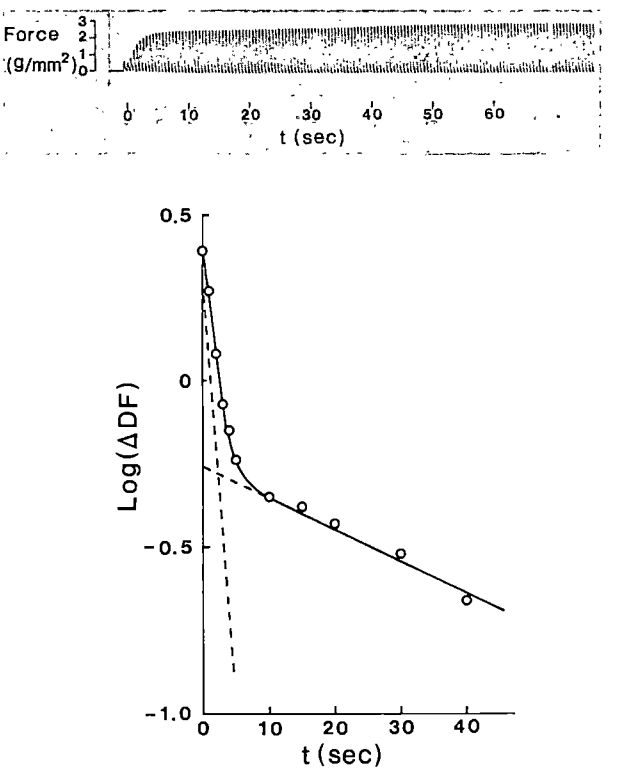


FIG 3. Time course of force increase following restimulation (at 2.0 Hz) of a briefly (1 minute) rested muscle. Top, Trace from strip-chart record. Prior to rest period, muscle was allowed to reach steady-state force of contraction at 0.1 Hz. Bottom, From data of strip-chart records logarithm of difference (ΔDF) between steady-state value and time t value of developed force was plotted against time. Dashed lines show fast and slow components. For this particular muscle preparation, DF = 2.94 − $1.91e^{-0.58t}$ − $0.55e^{-0.022t}$ [DF (g/mm^2) and t (sec)].

TABLE 2

Effect of Halothane on Decay of Potentiated State*

Halothane concentration	A	k_1	B	k_2	Overall half-life
%	g/mm^2	sec^{-1}	g/mm^2	sec^{-1}	sec
0 (n = 7)	0.46 ± 0.09	0.27 ± 0.04	1.60 ± 0.36	0.0057 ± 0.0004	75 ± 12
0.6 (n = 7)	0.62 ± 0.12	0.16 ± 0.01†‡ (59%)	0.77 ± 0.15§ (48%)	0.0072 ± 0.0006	20 ± 4§‖ (27%)
1.0 (n = 7)	0.40 ± 0.09	0.18 ± 0.03	0.44 ± 0.09§‖ (28%)	0.0085 ± 0.0014	21 ± 6§‖ (28%)

* Values are means ± SEM. A and B are magnitude constants, and k_1 and k_2 are first-order rate constants.
† $p < 0.05$ compared with control values (unpaired *t*-test).
‡ $p < 0.05$ compared with control values (paired *t*-test).
§ $p < 0.01$ compared with control values (paired *t*-test).
‖ $p < 0.01$ compared with control values (unpaired *t*-test).

TABLE 3

Effect of Length of Preceding Rest Period on Force Increase following Restimulation at 2.0 Hz*

Length of rest period	$DF_{steady\ state}$	A′	k_3	B′	k_4
min		g/mm^2	sec^{-1}	g/mm^2	sec^{-1}
1 (n = 7, except k_4, n = 5)†	2.37 ± 0.40	1.63 ± 0.33	0.67 ± 0.04	0.24 ± 0.08	0.027 ± 0.005
5 (n = 7)	2.36 ± 0.39	1.39 ± 0.30‖	0.67 ± 0.05	0.59 ± 0.09‡‖	0.035 ± 0.005
10 (n = 7)	2.37 ± 0.40	1.20 ± 0.25‖	0.68 ± 0.05	0.84 ± 0.12§‖	0.029 ± 0.003
20 (n = 7)	2.44 ± 0.45	1.21 ± 0.25‖	0.74 ± 0.08	0.94 ± 0.12§‖	0.028 ± 0.002

* Values are means ± SEM. Abbreviations used are: DF, developed force, A′ and B′, magnitude constants; k_3 and k_4, first-order rate constants.

† Rate constant k_4 could not be obtained for two muscles with B′ = 0.

‡ $p < 0.05$ compared with value obtained after 1 minute of rest (unpaired *t*-test).

§ $p < 0.01$ compared with value obtained after 1 minute of rest (unpaired *t*-test).

‖ $p < 0.01$ compared with value obtained after 1 minute of rest (paired *t*-test).

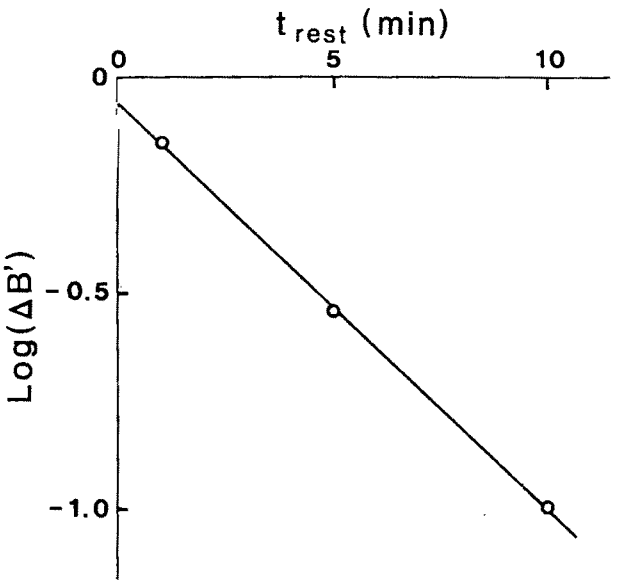


FIG 4. Increase in constant B′ accompanying increase in rest period (t_{rest}). Logarithm of difference (ΔB′) value at t_{rest} = 20 minutes (taken as final value) and t_{rest} = 1, 5, and 10 minutes were plotted against t_{rest}. From slope, rate constant 0.0036 sec^{-1} was obtained.

biphasic curve (Fig 3, bottom). The time course of the increase in developed force (DF) can be described by the equation:

$$DF = DF_{steady\text{-}state} - \underbrace{A'e^{-k_3t}}_{\text{(fast phase)}} - \underbrace{B'e^{-k_4t}}_{\text{(slow phase)}}$$

in which A′ and B′ are again, magnitude constants, and k_3 and k_4 are first-order rate constants (B′ = 0 when there is no slow phase). As can be seen in Table 3, increasing the length of time of rest period preceding restimulation resulted in marked increased in the magnitude of the slow phase (constant B′) and decrease in the magnitude of the fast phase (constant A′). The increase in the constant B′ accompanying the increase in the rest period was characterized by a rate constant of 0.0036 sec^{-1} (Fig 4). The rate constants (k_3 and k_4) and the final steady-state value of developed force were unaffected (Table 3). The effect of halothane was similar to the effect of increasing the rest period in that the anesthetic increased the magnitude of the slow phase (constant B′) and decreased the magnitude of the fast phase (constant A′). However, the effect of halothane was different in that the anesthetic decreased the final steady-state value of the developed force and the rate constants for both fast and slow phase (k_3 and k_4) (Table 4). The time course of force increase was invariably biphasic in the presence of halothane.

Discussion

The results of experiments reported in this paper indicate that halothane inhibits rested-state and potentiated-state contractions to a comparable degree. In the light of other work (8) concerning the importance of transsarcolemmally derived Ca^{2+} to force production during rested-state contractions, it can be inferred from our observation that halothane exerts an important action on the cell membrane to inhibit Ca^{2+} influx. This notion is supported by the work of Hauswirth (1) which shows that halothane shortens the cardiac action potential duration and by the work of Lynch et al (2) showing that halothane depresses the slow action potential, as well as by the work of Ohnishi et al (3) showing the reduction of La^{3+}-displaceable Ca^{2+} in the presence of halothane. The inability of the increased stimulation frequency under the conditions of paired-pulse stimulation to overcome halothane inhibition suggests that the anesthetic has an effect on the internal release of Ca^{2+} in addition to the effect on transsarcolemmal Ca^{2+} influx. Note that under the condition of single-pulse stimulation,

TABLE 4

Effect of Halothane on Force Increase following Restimulation at 2.0 Hz*

Halothane concentration	$DF_{steady\ state}$	A′	k_3	B′	k_4
%	g/mm^2		sec^{-1}	g/mm^2	sec^{-1}
0 (n = 12, except k_4, n = 7)†	2.17 ± 0.26	1.59 ± 0.22	0.52 ± 0.04	0.25 ± 0.07	0.028 ± 0.003
0.6 (n = 6)	1.54 ± 0.26‡ (71%)	0.70 ± 0.14‡§ (44%)	0.49 ± 0.07	0.60 ± 0.17§‖ (240%)	0.024 ± 0.004¶
1.0 (n = 7)	0.78 ± 0.12‡# (36%)	0.26 ± 0.04‡# (16%)	0.39 ± 0.03§ (75%)	0.39 ± 0.08	0.016 ± 0.003§¶ (57%)

* Values are means ± SEM. Abbreviations are defined in footnote to Table 3.

† Rate constant k_4 could not be obtained for five muscles with B′ = 0.

‡ $p < 0.01$ compared with control values (paired *t*-test).

§ $p < 0.05$ compared with control values (unpaired *t*-test).

‖ $p < 0.05$ compared with control values (paired *t*-test).

¶ Too few paired data for paired *t*-test.

$p < 0.01$ compared with control values (unpaired *t*-test).

Iwatzuki and Iwatzuki (15) have shown that increasing stimulation frequency does not reverse the negative inotropic effect of halothane. If the effect of halothane is limited to a competitive inhibition of transsarcolemmal Ca^{2+} influx, one might expect paired-pulse stimulation at an optimal frequency to overcome the negative inotropic effect of the anesthetic by maximizing the transsarcolemmal Ca^{2+} influx. The mode of interaction of Ca^{2+} and halothane in the myocardium appears to be more complex than simple competition for binding sites. Thus, competition has been demonstrated by double-reciprocal plot (16), but total reversal of halothane's negative inotropic effect is not possible even with large increases in extracellular Ca^{2+} concentration (17). Complete reversal of the negative inotropic effect of halothane by high concentrations of Ca^{2+} has so far been accomplished only under the condition of tetanus in the presence of caffeine (18). It is likely that in the presence of sufficiently high concentrations of caffeine, which is known to cause Ca^{2+} release from and to inhibit reuptake by internal stores (19), the effect of halothane on internally stored Ca^{2+} would be nullified and the remaining effect of halothane on transsarcolemmal Ca^{2+} influx could more readily be overcome by high extracellular Ca^{2+} concentration, by high stimulation frequency, and by the effect of caffeine itself (20) to increase transsarcolemmal Ca^{2+} influx.

The effect of halothane on the decay of potentiated state indicates that, in rabbit papillary muscle, the anesthetic reduces the magnitude of the major component of the potentiated state which decays slowly at a rate constant smaller than 0.01 sec^{-1} (14). Note that this component is present in muscle in mammalian species other than rabbit (21), whereas the minor, fast-decaying component appears to be unique to rabbit muscle [(14) and this study]. If the slow-decaying component represents the loss of Ca^{2+} from sarcoplasmic reticulum, the minor, fast-decaying component may represent the loss of Ca^{2+} from more labile, perhaps superficially located sites. Studies of ryanodine (22), and studies on the correlation between superficially bound Ca^{2+} and contractility (23), suggest that Ca^{2+} stored in sarcoplasmic reticulum plays a less important role in the contraction of rabbit ventricular muscle as compared with muscles from other mammalian species. Because of the disproportionately large effect of halothane on the magnitude of the slow-decaying, major component of the potentiated-state contraction, the relative contribution of the fast phase was magnified following exposure of muscles to the anesthetic, resulting in a shorter overall half-life. Thus, even though halothane had little effect on individual rate constants, the decay of potentiated state in rabbit muscle was accelerated by the anesthetic as was found earlier in cat muscle (6).

The time to reach a steady contractile state following an increase in the stimulation frequency (staircase) is known to be prolonged in the presence of halothane (15). In this regard, halothane resembles caffeine, which prolongs the time to reach a steady-state contraction following a change in stimulation frequency (24). The results of experiments on the effect of the length of the rest period preceding restimulation on the time course of force increase accompanying an increase in stimulation frequency indicate that the slow phase with rate constant k_4 most likely represents the filling of Ca^{2+} stores that were depleted during the rest period and the constant B′, the magnitude of empty store to be filled. The similarity in the magnitude of the rate constant for the changes in the constant B′ accompanying the increase in the rest

period (Fig 4) and the rate constant (k_2) for the decay of major component of potentiated state (Table 2) suggests that these rate constants reflect one and the same process, namely, the loss of internally stored Ca^{2+}.

It appears possible that the rate constant k_3 (Tables 3 and 4) describes the process of triggered release (25) of stored Ca^{2+}. Alternatively, the fast phase may represent filling by Ca^{2+} of sarcolemmal binding sites. These possibilities are not mutually exclusive, as the superficially bound Ca^{2+} may act as an activator of contraction (23) and as a trigger for release of internal Ca^{2+}. It should be recalled that Ong and Bailey (26) reported a biphasic increase in the Ca^{2+} content of the myocardium when a muscle maintained in a Ca^{2+}-free medium was exposed to a Ca^{2+}-containing medium, and suggested that the fast phase represents increase in trigger Ca^{2+} and the slow phase, the increase in activator Ca^{2+} in intracellular stores. As total depolarization time and, most likely, Ca^{2+} influx per unit time increase as the stimulation frequency is increased (14), the effects of increasing the stimulation frequency and that of increasing extracellular Ca^{2+} concentration are expected to be similar.

In conclusion, the results of the present study with intact rabbit papillary muscles strongly suggest that the effect of halothane on transsarcolemmal Ca^{2+} influx and the effect on stored Ca^{2+} contribute approximately equally to the negative inotropic effect of the anesthetic, and that halothane reduces the amount of stored Ca^{2+} by inhibiting uptake and accelerating the loss of the cation during rest.

REFERENCES

1. Hauswirth O. Effect of halothane on single atrial, ventricular, and Purkinje fibers. Circ Res 1969;24:745–50.
2. Lynch C, Vogel S, Sperelakis N. Halothane depression of myocardial slow action potentials. Anesthesiology 1981;55: 360–8.
3. Ohnishi ST, DiCamillo CA, Singer M, Price HL. Correlation between halothane-induced myocardial depression and decreases in La^{3+}-displaceable Ca^{2+} in cardiac muscle cells. J Cardiovasc Pharmacol 1980;2:67–75.
4. Su JY, Kerrick WG. Effects of halothane on caffeine-induced tension transients in functionally skinned myocardial fibers. Pfluegers Arch 1979;380:29–34.
5. Blanck TJJ, Thompson M. Calcium transport by cardiac sarcoplasmic reticulum: modulation of halothane action by substrate concentration and pH. Anesth Analg 1981;60:390–4.
6. Rusy BF. Influence of halothane and diethyl ether on the decay of potentiated state in mammalian myocardium. Anesthesiology 1980;53:S42.
7. Bass O. The decay of the potentiated state in sheep and calf ventricular myocardial fibers. Influence of agents acting on transmembrane Ca^{2+} flux. Circ Res 1976;39:396–9.
8. Lewartowski B, Prokopezuk A, Pytkowski B. Effect of inhibitors of slow calcium current on rested state contraction of papillary muscles and post rest contractions of atrial muscle of the cat and rabbit hearts. Pfluegers Arch 1978;377:167–75.
9. Craythorne NWB. The influence of anesthetics on the variability of myocardial contraction with heart rate. Anesthesiology 1968;29:182–3.
10. Penna M, Boye A, Novaković L. Effect of halothane on contractile function and reactivity of myocardium. Eur J Pharmacol 1970;10:151–60.
11. Goldberg AH, Phear WPC. The effect of halothane and paired electrical stimulation on isotonic contractions of isolated heart muscle. Anesthesiology 1969;30:341.
12. Blinks JR, Koch-Weser J. Analysis of the effects of changes in rate and rhythm upon myocardial contractility. J Pharmacol Exp Ther 1961;134:373–89.
13. Frost AA, Pearson RG. Kinetics and mechanisms. New York: John Wiley, 1953:149–51
14. Edman KAP, Jóhannsson M. The contractile state of rabbit papillary muscle in relation to stimulation frequency. J Physiol (Lond) 1976;254:565–81.
15. Iwatzuki N, Iwatzuki K. Effects of change in frequency of stimulation on myocardial depression produced by thiamylal and halothane. Tohoku J Exp Med 1975;117:119–24.
16. Price HL. Calcium reverses myocardial depression caused by halothane: site of action. Anesthesiology 1974;41:576–9.
17. Iwatzuki N, Iwatzuki K. Effects of changes in concentration of calcium on myocardial contractility depressed by thiamylal and halothane. Tohoku J Exp Med 1976;120:1–9.
18. Rusy BF. Effect of general anesthetics on the activation process in cardiac muscle: a study of the mechanism of anesthetic-induced myocardial depression. In: Fink BR, ed. Molecular mechanism of anesthesia. New York: Raven Press, 1975:625–36.
19. Weber AM, Herz R. The relationship between caffeine contracture of intact muscle and the effect of caffeine on reticulum. J Gen Physiol 1968;52:750–9.
20. Blinks JR, Olson CB, Jewell BR, Braveny P. Influence of caffeine and other methylxanthines on mechanical properties of isolated mammalian heart muscle: evidence for a dual mechanism of action. Circ Res 1972;30:367–92.
21. Morad M, Goldman Y. Excitation-contraction coupling in heart muscle: membrane control of development of tension. In: Butler JAV, Noble D, eds. Progress in biophysics and molecular biology. New York: Pergamon Press, 1973;27:257–313.
22. Sutko JL, Willerson JT. Ryanodine alteration of the contractile state of rat ventricular myocardium: comparison with dog, cat, and rabbit ventricular tissues. Circ Res 1980;46:332–43.
23. Bers DM, Philipson KD, Langer GA. Cardiac contractility and sarcolemmal calcium binding in several cardiac muscle preparations. Am J Physiol 1981;240:H576–83.
24. Henderson AH, Brutsaert DL, Forman R, Sonnenblick EH. Influence of caffeine on force development and force-frequency relations in cat and rat heart muscle. Cardiovasc Res 1974;8:162–72.
25. Fabiato A, Fabiato F. Calcium-induced release of calcium from the sarcoplasmic reticulum of skinned cells from adult human, dog, cat, rabbit, rat and frog hearts and from fetal and newborn rat ventricles. Ann NY Acad Sci 1978;307:491–522.
26. Ong SD, Bailey LE. Two functionally distinct calcium pools in the excitation-contraction coupling process. Experientia 1972; 28:1446–7.

ANESTH ANALG
1982;61:410-3

Dorsal Column Stimulation in Man: Facilitation of Primary Afferent Depolarization

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SHIMOJI, K., SHIMIZU, H., MARUYAMA, Y., MATSUKI, M., KURIBAYASHI, H., AND FUJIOKA, H.: Dorsal column stimulation in man: facilitation of primary afferent depolarization. Anesth Analg 1982;61:410-3.

The effects of cervical epidural dorsal column stimulation on the negative and slow positive waves of the spinal cord potentials recorded from the posterior epidural space at the lumbar enlargement, in response to intense stimulation of the tibial nerve in five neurologically normal subjects during neuroleptanesthesia were studied. Single pulses applied to the cervical dorsal cord near the midline produced slow positive potentials preceded by negative waves in the dorsal spinal cord at the level of the lumbar enlargement. The negative wave, believed to represent synchronized activities of interneurons, was inhibited up to 100 to 120 msec by conditioning dorsal column stimulation. The slow positive wave, thought to represent primary afferent depolarization, was facilitated for more than 100 msec with a transient inhibition for 10 to 40 msec. The results suggest that the pain-alleviating effect of dorsal column stimulation in man may be at least partly due to orthodromic and/or antidromic activation of descending inhibitory pathways which inhibit the responsible cells and facilitate primary afferent depolarization.

Key Words: SPINAL CORD: stimulation; PAIN: spinal cord stimulation.

DORSAL column stimulation (DCS) has become widely used for the control of chronic pain (1-8) and for rehabilitation of patients with neurologic diseases (9-14). However, although several hypotheses (15-20) have been proposed for the pain-inhibiting mechanism of DCS in animal experiments, little is known concerning the spinal mechanism that produces an analgesic effect during the application of DCS in man. Development of methods of recording the human spinal cord potential (SCP) safely from the epidural space, based on the technique of continuous epidural anesthesia (21), has provided the tool for the direct measurement of human spinal cord function as affected by DCS. We now first report the conditioning effect of epidural stimulation of the dorsal column applied at the cervical level on the segmentally evoked SCP recorded from the lumbar epidural space and evidence for the activation of an inhibitory system in the intact human spinal cord.

Methods

The subjects were five surgical patients, aged 16 to 25 years, suffering from scoliosis but free from neurologic deficits, who underwent spinal fusion under neuroleptanesthesia (60% nitrous oxide, 5 to 19 μg/kg of fentanyl and 0.25 mg/kg of droperidol). The neuroleptanesthesia has a slight depressive effect on SCP (22) but promotes hemodynamic stability during major surgery. Moreover, it was not feasible to subject the patients to repetitive painful stimuli in the awake state. For these reasons we performed our studies during general anesthesia using a neuroleptanesthesia technique.

Two pairs of epidural catheters were placed as close as possible to the midline, approximately 2 cm apart in the posterior epidural space at the levels of the cervical and lumbar enlargements, based on the technique of continuous epidural anesthesia (21). After placing the epidural electrodes at the lateral decubitus position, the subjects were placed in the supine position for recording and induction of anesthesia. Vital signs were measured and recorded every 5 minutes in order to maintain them within normal ranges. Elec-

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This study was supported by a grant from the Ministry of Health and Welfare, Tokyo, Japan.
Received from the Department of Anesthesiology, Niigata University School of Medicine, Asahi-machi 1-757, Niigata 951, Japan. Accepted for publication January 18, 1982. Presented in part at the Symposium on Indication of Spinal Cord Stimulation at the 7th International Congress of Neurosurgery, July 12-18, 1981, Munich.
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trode locations were verified by intraoperative roentgenograms. Evoked SCPs in response to ascending and descending volleys were recorded to monitor spinal cord function during surgical manipulations of and about the spinal cord. This procedure has been adopted routinely in our hospital to prevent spinal dysfunction caused by surgery. All procedures, risks, and benefits pertaining to the spinal cord potential monitoring during the surgery were explained to all patients participating in this study and to their families, and each signed an informed consent form. Observations were made before the start of the surgical manipulations on the spine. An intense tibial nerve stimulation (15 times threshold strength for evoking SCP) produced segmental SCP in the posterior epidural space at the level of the lumbar enlargement. At this stimulus intensity, awake patients always complained of sharp pain in a preliminary study. Segmentally evoked SCP consists of the initially positive spike (P_1), which is sometimes not recordable, and subsequent sharp negative wave (N_1), followed by slow positive waves (P_2) (Figure A), as previously reported elsewhere (23–25). The wave form and physiologic characteristics of the P_1, N_1, and P_2 potentials have been shown to be almost the same as, respectively, the initially positive spike, the slow negative, and the positive waves of SCP directly recorded from the dorsal cord surface in animals (26–32). The origins of the P_1, N_1, and P_2 waves of human SCP recorded epidurally, therefore, are thought to represent, respectively, incoming afferent volleys along the spinal roots, synchronous activities of the interneurons, and primary afferent depolarization (PAD) (24, 25). After setting the intensities of the epidural DCS (0.5 msec, 5 to 8 mamp) which produced a visible bilateral segmental muscle twitch, we injected pancuronium (0.1 mg/kg) intravenously and recorded SCPs during complete muscle relaxation.

Results

The preceding single pulses on the cervical epidural space, which themselves produced the spikes and slow negative-positive complexes in the lumbar enlargement (Figure, A), inhibited the N_1 wave up to 100 to 120 msec without affecting P_1. The P_2 wave was facilitated for more than 100 msec with transient inhibition for 10 to 40 msec after the cervical DCS (Figure, B). The maximum facilitatory effect of the DCS on the P_2 waves was seen at approximately 80 msec in two subjects and at approximately 50 msec in one subject after the conditioning stimulation. In the two remaining subjects, the segmentally evoked SCPs

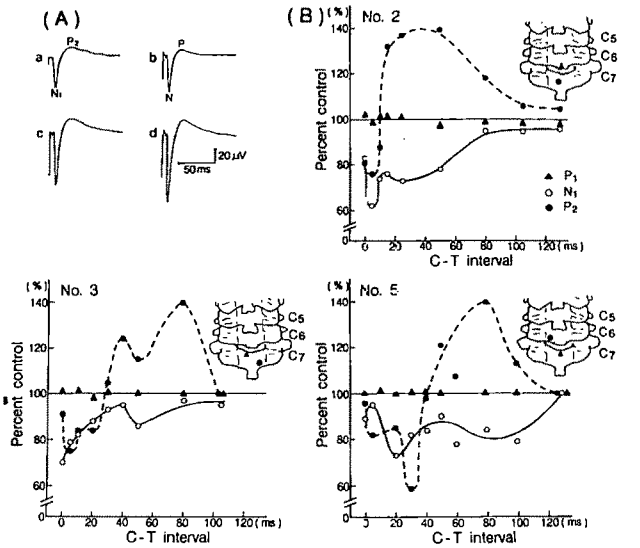


FIGURE. Suppression or facilitation of each component of segmentally evoked spinal cord potentials (SCPs) by conditioning stimulation applied to cervical enlargement from posterior epidural space. A, Specimen records of SCPs. a, Segmentally evoked SCP recorded from posterior epidural space at the lumbosacral enlargement (T-12) in response to tibial nerve stimulation (test stimulation). b, Slow negative-positive complex, recorded with same electrode as in a, produced by conditioning single pulses to cord dorsum from cervical posterior epidural space (C-7). c, Interacted SCPs produced by simultaneous stimulations of cervical cord and tibial nerve (conditioning and testing interval = 0). d, Simple summation of segmentally evoked SCP and potential produced by descending volley, constructed for easier calculation of degree of conditioning effect on segmentally evoked SCP. B, Time courses of suppression or facilitation of the negative (N_1) and slow positive (P_2) waves (ordinates) as a function of conditioning-testing (C-T) intervals (abscissa) in three subjects. Location of stimulating electrode is shown in right upper quadrant in each subject (▲, cathodal; ●, anodal). Note prolonged suppression of the N_1 and prolonged facilitation of P_2 after initial inhibition, and also considerable individual variations in configuration of recovery curves of N_1 as well as P_2 waves.

were not affected by the conditioning stimulation. In these two subjects, the conditioning pulses evoked the spikes but did not produce the slow negative-positive complexes in the lumbar enlargement (Table). Thus, the presence of the slow negative-positive complexes evoked by the descending volleys is thought to be essential for modulating the segmentally evoked SCP (Table). In other words, activation of the interneurons and PAD by descending volleys might be indispensable for modulation of the segmental phenomena in the human spinal cord. Differences in current distribution caused by the electrode positions as well as by individual variations of the anatomy of the cervical epidural space (33) must be considered in connection with the presence or absence of the slow negative-positive complexes in the lumbar enlargement evoked by the descending volleys.

TABLE

Patients with Locations of Cervical-Stimulating Electrodes, Conduction Velocities of Descending Volleys, and Presence or Absence of Slow Negative-Positive Complex

Subject no.	Age	Sex	Location of stimulating electrodes (distance from midline)*	Approx max conduction velocity along cord†	Presence of slow negative-positive complex
	yr		*mm*	*msec*	
1	14	F	R 12.5 R 11.2	88	No
2	13	M	L 1.0 R 2.0	72	Yes
3	13	F	R 3.0 L 4.0	81	Yes
4	10	M	R 9.0 R 7.8	87	No
5	18	F	L 0.5 R 4.2	77	Yes

* R and L denote shift of electrodes from midline to right and left sides, respectively. Cathodal electrode is shown in upper row in each pair.

† Approximate maximum conduction velocities were calculated by measuring latency of initial dip of spikes and distance between cervical stimulating electrodes (cathodal) and lumbosacral recording electrode (rostral) in posterior epidural space.

Discussion

In experimental animals, stimulation of the dorsal column (34, 35), the dorsolateral funiculus (36), or the nucleus raphe magnus with its nearby structures (37–39) has been known to inhibit activities of spinothalamic or laminae 4 and 5 cells, and to facilitate those of substantia gelatinosa cells (30). Although it is difficult to determine whether excitatory or inhibitory interneurons contribute to segmentally evoked negative (N_1) waves in the human SCP, several pharmacologic studies (22–24) indicate that the majority of N_1 components are composed of excitatory neurons. Thus, inhibition of the N_1 wave and facilitation of the P_2 wave in the present study probably reflect mainly a suppressive effect on excitatory neurons and augmentation of presynaptic inhibitory action, respectively, in human spinal cord via antidromic activation of dorsal columns. Orthodromic activation of dorsolateral funiculus and other descending tracts due to current spread may partly contribute to the inhibition (35). Besides interactions at an interneuronal level, dorsal column volleys are presumed to collide with afferent inputs projecting up the dorsal column (35). However, collision may not be importantly involved in modulation of pain in the present study, as the P_1 wave which is believed to represent afferent input was unchanged by epidural dorsal column stimulation. Alternatively, ascending volleys in the dorsal column or in other pathways could interfere with pain afferents in the supraspinal structures (40).

In a preliminary study (6), we could not detect any change in the SCP recorded with the same electrodes as the stimulating electrodes after the termination of low-frequency epidural DCS, even though a considerable degree of analgesic effect remained for several minutes. Therefore, we thought that such a slowly developing and slowly regressing analgesic effect might not be related to the spinal phenomena. Taking our preliminary and present experiments together, the data suggest that there may be two pain inhibitory mechanisms produced by DCS in intact man: the phasic and tonic. The phasic inhibition of pain may be manifest at the spinal segmental level by a relatively high frequency stimulation of the dorsal column. The fact that the P_2 wave, which is a reflection of PAD (24, 25), was maximally facilitated at 50 to 80 msec after the conditioning stimulation of the upper segments, may indicate that the maximum phasic inhibitory effects of DCS are exerted by 12.5 to 20 Hz stimuli which influence the lower spinal segments.

Another important finding in the present study is that descending volleys evoked by epidural DCS could produce the slow negative and positive complexes in the lumbar enlargement, the configurations of which are similar to the N_1 and P_2 waves, respectively, of segmentally evoked SCP. This may indicate that inhibitory interneurons, reflected as a part of the negative wave, and PAD, demonstrated as the slow positive wave, are activated by descending volleys and then modulate the afferent impulses at the spinal segments in man.

REFERENCES

1. Shealy CN, Mortimer JT, Hagfors NR. Dorsal column electroanalgesia. J Neurosurg 1970;32:560–4.
2. Nashold BS, Friedmann H. Dorsal column stimulation for control of pain. J Neurosurg 1972;36:590–7.
3. Hymes AC, Raab DE, Yonehiro EG, Nelson GD, Printy AL. Acute pain control by electrostimulation: a preliminary report. Adv Neurol 1974;4:761–7.
4. Krainick JU, Thoden U. Electrical stimulation of the spinal cord for the relief of pain: method-patient selection-clinical results. Adv Neurosurg 1975;4:210–5.
5. Shimoji K, Higashi H, Kano T, Asai S, Morioka T. Electrical management of intractable pain. Jpn J Anesthesiol 1971;20:444–7.
6. Shimoji K, Kitamura H, Ikezono E, Shimizu H, Okamoto K, Iwakura Y. Spinal hypalgesia and analgesia by low-frequency electrical stimulation in the epidural space. Anesthesiology 1974;41:91–4.
7. Shimoji K, Matsuki M, Shimizu H, et al. Low-frequency, weak extradural stimulation in the management of intractable pain. Br J Anaesth 1977;49:1081–8.
8. Doerr M, Krainick J-U, Thoden U. Pain perception in man

after long term spinal cord stimulation. J Neurol 1978;271:261–70.
9. Cook AW, Weinstein S. Chronic dorsal column stimulation in multiple sclerosis: preliminary report. NY State J Med 1973;73:2368–72.
10. Dooley DM, Sharkey J, Keller W, Kasprak M. Treatment of demyelinating and degenerative diseases by electrostimulation of the spinal cord. Med Prog Technol 1978;6:1–14.
11. Siegfried J, Krainick J-U, Haas H, Adorjani C, Meyer M, Thoden U. Electrical spinal cord stimulation for spastic movement disorders. Appl Neurophysiol 1978;41:134–41.
12. Illis LS, Sedgwick EM, Oygar AE, Awadalla MA. Dorsal column stimulation in the rehabilitation of patients with multiple sclerosis. Lancet 1976;1:1383–6.
13. Maruyama Y, Shimizu H, Endo H, Shimoji K. Effect of low frequency, weak extradural stimulation on SMON patients. In: Shigematsu I, ed. Bibliographies in researchs for SMON, 1979. Tokyo Ministry of Health and Welfare, 1979:150–5.
14. Read DJ, Mathews WS, Higson RH. The effect of spinal cord stimulation on function in patients with multiple sclerosis. Brain 1980;103:803–33.
15. Melzack R, Wall PD. Pain mechanisms: a new theory. Science 1965;150:971–9.
16. Emmers R, Ruderman MI. Inhibition at the T cells of the spinothalamic tract: a neurophysiological basis for electrically induced analgesia. Proc Soc Exp Biol Med 1974;145:1310–6.
17. Bantli H, Bloedel JR, Thienprasit P. Supraspinal interactions resulting from experimental dorsal column stimulation. J Neurosurg 1975;42:296–300.
18. Kerr FWL. Pain: a central inhibitory balance theory. Mayo Clin Proc 1975;50:685–90.
19. Basbaum AI, Clanton CH, Fields HL. Opiate and stimulus-produced analgesia: functional anatomy of a medullospinal pathway. Proc Natl Acad Sci USA 1976;73:4685–8.
20. Fields HL, Basbaum AI. Brain stem control of spinal pain-transmission neurons. Ann Rev Physiol 1978;40:217–48.
21. Shimoji K, Higashi H, Kano T. Epidural recording of spinal electrogram in man. Electroencephalogr Clin Neurophysiol 1971;30:236–9.
22. Shimoji K, Kano T. Evoked electrospinogram: interpretation of origin and effects of anesthetics. In: Mori K, ed. Effect of anesthesia on the central nervous system. Boston: Little, Brown, 1975:171–89.
23. Shimoji K, Kano T, Higashi H, Morioka T, Henschel ED. Evoked spinal electrograms recorded from epidural space in man. J Appl Physiol 1977;33:468–71.
24. Shimoji K, Ito Y, Ohama K, Sawa T, Ikezono E. Presynaptic inhibition in man during anesthesia and sleep. Anesthesiology 1975;43:388–91.
25. Shimoji K, Matsuki M, Ito Y, et al. Interactions of human cord dorsum potential. J Appl Physiol 1976;40:79–84.
26. Barron DH, Matthews BHC. The interpretation of potential changes in the spinal cord. J Physiol (Lond) 1938;92:276–321.
27. Koketsu K. Intracellular potential changes of primary afferent nerve fibers in spinal cord of cats. J Neurophysiol 1956;19:375–92.
28. Wall PD. Excitability changes in afferent fibre terminations and their relation to slow potentials. J Physiol (Lond) 1958;142:1–21.
29. Eccles JC. The physiology of synapses. New York: Springer-Verlag, 1964:220–38.
30. Wall PD. The substantia gelatinosa: a gate control mechanism set across a sensory pathway. Trends in Neurosciences 1980;3:221–4.
31. Carpenter DO, Rudomín P. The organization of primary afferent depolarization in the isolated spinal cord of the frog. J Physiol (Lond) 1973;229:471–93.
32. Willis WD, Núnez R, Rudomín P. Excitability changes in terminal arborizations of single Ia and Ib afferent fibers produced by muscle and cutaneous conditioning volleys. J Neurophysiol 1976;39:1150–9.
33. Bromage PR, Epidural analgesia. Philadelphia: WB Saunders, 1978:8–67.
34. Hillman P, Wall PD. Inhibitory and excitatory factors influencing the receptive fields of lamina 5 spinal cord cells. Exp Brain Res 1969;9:284–306.
35. Foreman RD, Beall JE, Applebaum AE, Coulter JD, Willis WD. Effects of dorsal column stimulation on primate spinothalamic tract neurons. J Neurophysiol 1976;39:534–46.
36. Dubuisson D, Wall PD. Descending influences on receptive fields and activity of single units recorded in laminae 1, 2 and 3 of cat spinal cord. Brain Res 1980;199:283–98.
37. McGreery DB, Bloedel JR, Hames EG. Effects of stimulating in raphe nuclei and in reticular formation on response of spinothalamic neurons to mechanical stimuli. J Neurophysiol 1979;42:166–82.
38. Sessle BJ, Hu JW, Dubner R, Lucier GE. Functional properties of neurons in cat trigeminal subnucleus caudalis (medullary dorsal horn). II. Modulation of responses to noxious and nonnoxious stimuli by periaqueductal gray, nucleus raphe magnus, cerebral cortex, and afferent influences, and effect of naloxone. J Neurophysiol 1981;45:193–207.
39. Gerhart KD, Wilcox TK, Chung JM, Willis WD. Inhibition of nociceptive and nonnociceptive responses of primate spinothalamic cells by stimulation in medial brain stem. J Neurophysiol 1981;45:121–36.
40. Salibi NA, Saadé NE, Banna NR, Jabbur SJ. Dorsal column input into the reticular formation. Nature 1980;288:481–3.

ANESTH ANALG
1982;61:414-7

Epinephrine-Induced Arrhythmias during Halothane Anesthesia with the Addition of Nitrous Oxide, Nitrogen, or Helium in Dogs

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LIU, W.-S., WONG, K. C., PORT, J. D., AND ANDRIANO, K. P.: Epinephrine-induced arrhythmias during halothane anesthesia with the addition of nitrous oxide, nitrogen, or helium in dogs. Anesth Analg 1982;61:414-7.

The arrhythmogenicity of epinephrine was examined in 34 male mongrel dogs awake and during 1.1 MAC steady-state halothane-O_2 anesthesia with the addition of 50% N_2O, nitrogen, or helium. All anesthetized dogs required more epinephrine than did awake dogs to produce ventricular extrasystoles. Dogs given halothane-N_2O were more sensitive to the epinephrine infusion than those given halothane-nitrogen or halothane-helium. The dogs given halothane-N_2O also showed a small, but statistically significant difference from dogs given halothane-O_2. These results suggest that the addition of N_2O to halothane increases the cardiac arrhythmic potential of epinephrine in the dog.

Key Words: HEART: arrhythmia, epinephrine-induced; ANESTHETICS, Volatile: halothane; ANESTHETICS, Gases: nitrous oxide; GASES: nitrous oxide, nitrogen, helium.

IN A RECENT publication (1), we compared the arrhythmogenicity of epinephrine in dogs anesthetized with halogenated agents (halothane, enflurane, and methoxyflurane) with N_2O as an adjunct. We found the arrhythmogenic doses of epinephrine were considerably smaller than those reported when N_2O was not used with halothane, enflurane, or methoxyflurane (2, 3). Nitrous oxide alone is known to have an adrenergic stimulatory effect (4). The addition of N_2O to halothane (5, 6), ether (7), and morphine (8) in man produces a predominant alpha-adrenergic stimulation manifested by an increase in peripheral vascular resistance and a decrease in cardiac performance. Thus, the addition of N_2O to a potent anesthetic might potentiate cardiac arrhythmias induced by an overactive sympathetic nervous system.

Helium and nitrogen are useful inhalational adjuncts in certain clinical situations. Helium, by promoting laminar airflow, improves pulmonary ventilation when the upper airway is compromised (9); whereas nitrogen is commonly used to reduce the inspired concentration of oxygen delivered to neonates or premature infants. The purpose of this study was to evaluate the arrhythmogenicity of epinephrine in dogs anesthetized with halothane, to which N_2O, N_2, or helium was added to the inspired gas mixture.

Methods

Thirty-four male mongrel dogs, weighing 18 to 25 kg each, were used for this study. Twelve animals served as awake control animals following instrumentation after injection of intravenous thiopental, 15 to 20 mg/kg. Experimental data were collected at least 90 minutes after the intravenous thiopental. In the 22 anesthetized animals, tracheal intubation was facilitated by intravenous thiopental, 20 to 30 mg/kg, and mechanical ventilation maintained $P_{a_{CO_2}}$ levels between 32 to 38 torr. A femoral arterial catheter provided continuous pressure monitoring and blood gas sampling. Anesthesia was maintained with 1.1 MAC (altitude adjusted) halothane. The end-tidal concentrations of halothane, inspired concentration of O_2,

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Received from the Department of Anesthesiology, University of Utah School of Medicine, Salt Lake City, Utah. Accepted for publication January 6, 1982.
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lead II electrocardiogram (ECG), heart rate, arterial blood pressure, and esophageal temperature were monitored continually. Esophageal temperature was kept at 37 ± 1°C. Ringer's lactate solution was infused to maintain mean arterial pressures between 80 to 100 torr before the administration of epinephrine. Epinephrine (5 μg/ml) was infused at a rate of 1 μg/kg/min; if ventricular arrhythmias did not develop after 10 minutes, the infusion was discontinued for 20 minutes and restarted at 2 μg/kg/min. The ventricular arrhythmic threshold dose (micrograms per kilogram) was the dose of epinephrine at which four or more continuous or intermittent ventricular extrasystoles appeared within 15 seconds. Twenty-two animals were studied under the following four experimental conditions: 100% O_2, 50% N_2O-O_2, 50% N_2-O_2, and 50% He-O_2, in addition to a steady state of 1.1 MAC halothane. Each anesthetic regimen was allowed 1 hour for equilibration before its arrhythmogenicity was evaluated and the order of administration of the four regimens was randomized (Latin square).

Comparison of arrhythmic threshold doses, mean arterial pressures, and changes in heart rate among the four regimens was done by one-way analysis of variance for repeated measurements. Individual comparisons among the four regimens were performed by the Scheffe confidence interval test. Unpaired *t*-test was used to determine statistical differences between awake dogs and anesthetized dogs; $p \leq 0.05$ was considered statistically significant.

Results

Results are summarized in the Table. The null hypothesis for equal arrhythmic doses among the four regimens was rejected ($F_{3,63} = 3.37$; $p < 0.025$). The Scheffe confidence interval test for significance of differences in arrthymia threshold doses of epinephrine showed that halothane-O_2 > halothane-N_2 = halothane-helium > halothane-N_2O. The epinephrine arrhythmic threshold dose of 1.57 ± 0.15 μg/kg in awake dogs was significantly lower ($p < 0.001$) than in anesthetized dogs. Dogs given halothane-N_2O had an arrhythmic threshold dose of 3.39 ± 0.35 μg/kg, which was significantly lower ($p < 0.05$) than in dogs given halothane-O_2 (4.25 ± 0.36 μg/kg) and also significantly different from the arrhythmic threshold doses in dogs given halothane-N_2 (3.84 ± 0.39 μg/kg) or halothane-helium (4.01 ± 0.41 μg/kg). The increases in mean arterial pressures were not significantly different among the anesthetized groups; likewise decreases of heart rate during peak mean arterial pressures, which varied from 10 to 50 beats per minute, also were not significantly different among the anesthetized groups. However, the bradycardia observed in awake dogs was significantly different ($p < 0.001$) from that seen in anesthetized dogs. None of the dogs died during the course of this study.

Discussion

The use of epinephrine as an arrhythmogenic agent for testing sensitivity to arrhythmias is clinically meaningful because intraoperative arrhythmias are frequently associated with an imbalance of the autonomic nervous system, usually a predominance of the sympathetic over the parasympathetic nervous system. Factors (10) known to increase the potential for development of catecholamine-induced arrhythmias include hypoxia, hypercarbia, hypertension, and heart rate (11). Although the Pa_{O_2} levels in our awake dogs while breathing room air were lower than those in anesthetized dogs, none of the arterial O_2 saturations were less than 95%. The Pa_{CO_2} levels of all groups of

TABLE

Arrhythmic Threshold Dose of Epinephrine and Concurrent Changes in Blood Pressure and Heart Rate*

Group	N	Epinephrine threshold dose	Increase in MAP	Change in heart rate during peak MAP
		μg/kg	*torr*	*beats/min*
Awake-control, room air	12	1.57 ± 0.14†	60.5 ± 9.7	−19.0 ± 3.2†
Halothane-O_2	22	4.25 ± 0.36	46.9 ± 7.3	−28.1 ± 6.0
Halothane-He 50%-O_2	22	4.01 ± 0.41‡	51.8 ± 6.2	−32.0 ± 6.1
Halothane-N_2 50%-O_2	22	3.84 ± 0.39‡	52.9 ± 7.0	−33.2 ± 5.0
Halothane-N_2O 50%-O_2	22	3.39 ± 0.35‡§	55.0 ± 8.2	−31.1 ± 7.6

* Values are means ± SEM.

† $p < 0.001$ compared with the anesthetized groups.

‡ $p < 0.05$ compared with halothane-O_2.

§ $p < 0.05$ compared with halothane-N_2-O_2 and halothane-He-O_2.

dogs were between 32 to 38 torr. Similarly, changes in mean arterial pressures and heart rates also were not significantly different among the experimental groups. Therefore, these factors did not appear to be significant variables in our study.

We did not vagotomize the animals because of the need to reuse them and because we wished to study a preparation comparable to the clinical setting. Dogs that have been treated with atropine tend to exhibit supraventricular tachycardia in response to epinephrine infusion rather than ventricular extrasystoles and bigeminal rhythm (12). In contrast, atrial pacing to a critical tachycardic level of vagotomized dogs during epinephrine infusion may induce bigeminy (11). There appear to be differences between surgical and chemical vagotomy in the anesthetized dog.

The addition of N_2O to halothane-oxygen anesthesia in man produces vasoconstriction and other evidence of sympathetic stimulation (5, 6). Data obtained from cats anesthetized with halothane-N_2O-O_2 suggest that the sympathetic stimulation of N_2O is exerted at suprapontine levels and that the direct effect of N_2O is depressant to vasomotor neurons at the brainstem or spinal level (13). The interaction of N_2O and halogenated anesthetics or narcotics generally results in vasoconstriction and cardiac depression (5–8). Our results are compatible with the clinical impression that intraoperative cardiac arrhythmias can often be aborted by eliminating N_2O as an adjunct to halothane anesthesia.

There are no published data on the effects of N_2 on cardiac rhythm. The data obtained in our awake control animals, breathing 80% N_2-20% O_2, suggest minimal antiarrhythmic properties against epinephrine-induced arrhythmias. However, Joas and Stevens[14] reported an epinephrine arrhythmic dose of 36 μg/kg in the awake dog, a dose much larger than our 1.57 μg/kg. This apparent discrepancy can be attributed to their method of infusion of epinephrine which included the administration of a predetermined dose of epinephrine over a 60-second period. It is noteworthy that 24 of 29 animals in their study died from ventricular fibrillation or of intercurrent disease. It is unlikely that their arrhythmic dose of epinephrine represented a threshold dose.

There is also a paucity of publications on the use of helium as an antiarrhythmic agent. Pifarré et al (15) reported a reduction in the incidence of ventricular fibrillation in dogs ventilated by He-O_2 following acute myocardial infarction produced by ligation of the left circumflex coronary artery. Likewise, Raymond et al (16) also reported a reduction of cardiac arrhythmias in dogs breathing He-O_2 after ligation of the circumflex coronary artery. However, in dogs not subjected to circumflex ligation, Raymond et al (16) did not observe differences in the frequency of epinephrine-induced extrasystoles when dogs anesthetized with pentobarbital were given helium or N_2. Notwithstanding, Holland et al (17), using a similar experimental technique, failed to demonstrate any cardiac protective effect of helium. When cardiac arrhythmias are caused by hypoxia secondary to obstruction of upper airway, helium might be helpful to improve pulmonary ventilation (9) and cardiac oxygenation.

The epinephrine threshold dose in dogs given halothane-N_2O was significantly lower ($p < 0.05$) than in dogs given halothane-O_2. Although the epinephrine threshold dose in dogs given halothane-N_2O was also statistically significantly lower than in dogs given halothane-N_2 or halothane-helium, the difference was small and probably not significant physiologically. These results suggest that the addition of N_2O to halothane increases the potential for development of epinephrine-induced arrhythmias.

REFERENCES

1. Puerto BA, Wong KC, Puerto AX, Tseng CK, Blatnick RA. Epinephrine-induced dysrhythmias: comparison during anaesthesia with narcotics and with halogenated inhalation agents in dogs. Can Anaesth Soc J 1979;26:263–8.
2. Munson ES, Tucker WK. Doses of epinephrine causing arrhythmia during enflurane, methoxyflurane and halothane anaesthesia in dogs. Can Anaesth Soc J 1975;22:495–501.
3. Zahed B, Miletich DJ, Ivankovich AD, Albrecht RF, Toyooka ET. Arrhythmic doses of epinephrine and dopamine during halothane, enflurane, methoxyflurane, and fluroxene anesthesia in goats. Anesth Analg 1977;56:207–10.
4. Eisele JH, Smith NT. Cardiovascular effects of 40 percent nitrous oxide in man. Anesth Analg 1972;51:956–63.
5. Smith, NT, Eger EI II, Stoelting RK, Whayne TF, Cullen D, Kadis LB. The cardiovascular and sympathomimetic responses to the addition of nitrous oxide to halothane in man. Anesthesiology 1970;32:410–21.
6. Bahlman SH, Eger EI II, Smith NT, et al. The cardiovascular effects of nitrous oxide-halothane anesthesia in man. Anesthesiology 1971;35:274–85.
7. Smith NT, Eger EI II, Gregory GA, Cullen BF, Cullen DJ. The cardiovascular responses to the addition of nitrous oxide to diethyl ether in man. Can Anaesth Soc J 1972;19:42–8.
8. Wong KC, Martin WE, Hornbein TF, Freund FG, Everett J. The cardiovascular effects of morphine sulfate with oxygen and with nitrous oxide in man. Anesthesiology 1973;38:542–9.
9. Lu TS, Ohmura A, Wong KC, Hodges MR. Helium-oxygen in treatment of upper airway obstruction. Anesthesiology 1976;45:678–80.
10. Katz RL, Epstein RA. The interaction of anesthetic agents and adrenergic drugs to produce cardiac arrhythmias. Anesthesiology 1968;29:763–80.

11. Zink J, Sasyniuk BI, Dresel PE. Halothane-epinephrine-induced cardiac arrhythmias and the role of heart rate. Anesthesiology 1975;43:548–55.
12. Wong KC, Wyte SR, Martin WE, Crawford EW. Antiarrhythmic effects of skeletal muscle relaxants. Anesthesiology 1971;34:458–62.
13. Fukunaga AF, Epstein RM. Sympathetic excitation during nitrous oxide-halothane anesthesia in the cat. Anesthesiology 1973;39:23–36.
14. Joas TA, Stevens WC. Comparison of the arrhythmic doses of epinephrine during Forane, halothane and fluroxene anesthesia in dogs. Anesthesiology 1971;35:48–53.
15. Pifarré R, Raghunath TK, Vanecko RM, Chua FS, Balis JR, Neville WE: Effect of oxygen and helium mixtures on ventricular fibrillation. J Thorac Cardiovas Surg 1970;60:648–52.
16. Raymond L, Weiskopf RB, Halsey MJ, Goldfien A, Eger EI II, Severinghaus JW. Possible mechanism for the antiarrhythmic effect of helium in anesthetized dogs. Science 1972;176:1250–2.
17. Holland JA, Wolfe WG, Kylstra JA. Helium: absence of antiarrhythmic effect in anesthetized dogs. J Thorac Cardiovas Surg 1973;66:478–80.

Epidural Beta-Endorphin in Treatment of Pain

Synthetic beta-endorphin, 3 mg in 10 ml of normal saline, was injected epidurally in 10 patients with intractable pain due to disseminated cancer. All patients reported relief of pain. Relief was obtained within a mean of 24.9 ± 3.4 (SE) minutes (range 9 to 45 min). The mean duration of analgesia was 19 ± 3 hours. No new symptoms were reported. There were no blood gas tension changes, hypotension, hypothermia, catatonia, or muscle rigidity. The degree of analgesia produced was less than that previously reported following intrathecal beta-endorphin administration. (*Oyama T, Fukushi S, Jin T. Epidural β-endorphin in treatment of pain. Can Anaesth Soc J 1982;29:24–6*)

ANESTH ANALG
1982;61:418-22

A Model for Comparison of Local Anesthetics in Man

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McQuay, H., Weir, L., Porter, B., O'Sullivan, G., Paterson, G., Moore, A., and Bullingham, R.: A model for comparison of local anesthetics in man. Anesth Analg 1982;61:418-22.

Ten patients scheduled for bilateral arm surgery were given general anesthesia plus, on one side, an axillary brachial plexus block. Ten additional patients scheduled for bilateral foot surgery were similarly given general anesthesia plus an ankle block on one side. A within-patient blind comparison of postoperative analgesia between blocked and unblocked side was performed. An additional 10 patients scheduled for bilateral foot surgery had one side blocked with lidocaine and the other side blocked with bupivacaine for comparison of postoperative analgesia. Postoperative analgesia recorded by a nurse observer was significantly better on the blocked side compared with the unblocked side. This difference was greater for ankle blocks. There were no differences between the analgesic measures for lidocaine and bupivacaine ankle blocks over the 6-hour study period.

Key Words: PAIN: postoperative; ANESTHETICS, Local: bupivacaine, lidocaine; ANESTHETIC TECHNIQUES, Regional: axillary, ankle.

COMPARISON of local anesthetics in patients suffering from pathologic pain has not been subject to the intensive study imposed on new analgesics. The clinical choice of a particular local anesthetic is commonly made on the basis of relative toxicities, mechanism of metabolism, and the single analgesic factor of duration of action. With systemic analgesics, a controlled comparison of analgesic properties in a relevant clinical context is considered to be mandatory. In particular, these properties would include some measure of the quality of analgesia as well as duration of action and time of onset. With local anesthetics, the assumption seems to be made that this quality is the same for all the drugs. Comparison of integrated analgesic effect would provide the validation of this assumption.

The design of clinical trials for the study of local anesthetics is not straightforward. Trials of systemic analgesics are designed to include placebo groups so that analgesic effect measured after the test treatment may be compared with the degree of analgesia reported in the placebo group. The use of placebo medication in trials of local anesthetics presents ethical difficulties; however, comparison with an equivalent of the placebo group is necessary to preclude false attribution of analgesic effect to administration of the test local anesthetic. Trials that compare the effects of drugs for a particular block require technically equivalent blocks for each patient in the study. Trials that compare patients who have received local blocks with patients who have received systemic analgesics need a double-blind double-dummy design for within-patient comparison, or large numbers of patients for between-patient comparison.

The present study describes a within-patient model for comparison of the analgesia that results from nerve blocks. The model allows comparison to be made, both between the additional analgesia provided by a block over the analgesia resulting from opiate premedication and the general anesthetic, and between blocks made with different local anesthetics. Because the comparisons are made within the same

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Financial support provided by Duncan Flockhart.
Received from the Nuffield Departments of Anaesthetics and Clinical Biochemistry, John Radcliffe Hospital and Radcliffe Infirmary, Oxford, England. Accepted for publication January 6, 1982.
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patient, analytical methods used and validated in the testing of analgesic compounds are applicable, and the trials do not require large numbers of patients.

Patients and Methods

The 30 patients studied were undergoing elective bilateral minor orthopedic surgery of the limbs at the Nuffield Orthopaedic Centre, Oxford. The surgical procedure was the same on both limbs. Ethical approval for the study was granted by the appropriate committee. Consent was obtained from healthy patients between the ages of 18 and 70 years and weighing between 45 and 90 kg. Patients suffering from known severe cardiovascular disease were excluded as were those incapable of adequate communication with the nurse observer. The operative procedure for the upper limb was predominantly carpal tunnel release, and for the lower limb the procedures were Keller's and Mitchell's operations.

All patients received the same premedication and general anesthetic. An opiate, papaveretum, 15 mg, and hyoscine, 0.3 mg, were given intramuscularly 1 hour prior to surgery, approximately 45 minutes before the blocks were performed. Anesthesia was induced with intravenous thiopental, 5 mg/kg, and maintained with spontaneous breathing of nitrous oxide and oxygen (2:1) with halothane 0.5% to 2%. A Bain circuit and facemask were used, with total fresh gas flow of 100 ml/kg. No supplementary opiate was given.

Local anesthetic blocks were performed by an experienced anesthetist in the anesthetic room after the patient was asleep. The side to be blocked was indicated on a card in a sealed envelope. The order had been randomized; the same number of blocks was performed on each side. The nurse observer was not present during performance of the block and there was no visible indication of the blocked side.

The trial design was controlled and blind between the patient and the observer. The same trained nurse observer (L.W.) made all the observations. The 30 patients were allocated to one of three groups. Ten patients undergoing bilateral surgery of the upper limb entered the arm block versus no arm block group (Arm group). The first 10 patients having bilateral foot surgery entered the ankle block versus no block group (Ankle group). The next 10 patients having bilateral foot surgery entered the bupivacaine versus lidocaine group (BVL group).

Patients in the Arm group received an axillary brachial plexus block (1) on the prescribed side. With the arm abducted to 90°, without tourniquet, and using the axillary pulse as landmark, 30 ml of bupivacaine 0.5% plain solution was injected periarterially into the neurovascular sheath.

Patients in the Ankle group received an ankle block (2) on the prescribed side. For each patient, 2.5 ml of bupivacaine 0.5% plain solution was injected to block the saphenous nerve, 2.5 ml to block the deep peroneal nerve, 5 ml to block the tibial nerve, and 10 ml to block the superficial peroneal nerve (total volume 20 ml).

Patients in the BVL group received ankle blocks on both sides. One side was blocked with bupivacaine 0.5%, the other side with the same volume of 1% lidocaine plain solution using the same technique as described above for the Ankle group. The choice of which agent for which side was indicated on a card in a sealed envelope. The order was randomized; with each agent the same number of blocks was performed on each side. Patients heavier than 70 kg received a total volume of 20 ml on each side (as for the Ankle group above). Those weighing between 50 and 70 kg received 2 ml to the saphenous nerve, 1.5 ml to the deep peroneal nerve, 4 ml to the tibial nerve, and 7.5 ml to the superficial peroneal nerve (total 15 ml on each side). The respective volumes for those weighing less than 50 kg were 1.25, 1.25, 2.5, and 5 ml (total 10 ml on each side).

After surgery the patients were taken to the recovery ward where they stayed for the duration of the study. The same trained nurse observer (L.W.) looked after all the patients during the study and made all the measurements. Pain intensity was measured on a four-point scale (0, none; 1, slight; 2, moderate; 3, severe) separately for each side 1.5, 2.5, 3.5, 4.5, 5, 5.5, 6, 6.5, 7, and 7.5 hours after the blocks were performed. Pain relief, measured on a five-point scale (0, none; 1, fair; 2, moderate; 3, a lot; 4, complete), was measured at the same times. Ten-centimeter visual analogue lines for pain intensity and pain relief were also presented to the patients at the same times. These were marked by the patients in the Ankle and BVL groups, and by the nurse observer for the patients in the Arm group. Vital signs were recorded by the nurse observer.

Inadequate analgesia from either side was treated with 15 mg of papaveretum given intramuscularly. The time to next analgesic from when the block was performed was recorded for each patient.

Analysis of Results

Pain intensity, pain relief, visual analogue pain intensity, and visual analogue pain relief scale indices

were analyzed for both limbs. An area under the curve against time (AUC) was calculated using a trapezoidal rule for each of these indices. This produced AUC pain intensity (AUC-PI), AUC pain relief (AUC-PR), AUC visual analogue pain intensity (AUC-VAS-PI), and AUC visual analogue pain relief (AUC-VAS-PR) for each limb. The initial values of these indices differ from their equivalents in systemic analgesic trials (3) where test medications are given to patients in established pain; in this trial the initial value for pain intensity was expected to be low, and that for pain relief high because the block had been performed before the analgesic measurements began.

For each group, these derived measures were compared for each patient with similarly blocked or unblocked limbs using the Wilcoxon matched pairs signed-ranks test. Statistical significance was assessed on a one-tail test for the Arm and Ankle groups in which the direction of differences was predicted, and on a two-tail test for the BVL group. The times to next analgesic for the three groups were compared using the Mann-Whitney U-test.

Results

Arm Group

The demographic data and results of the analgesic measures for the Arm group are presented in Table 1. One patient was omitted from all analyses because he inadvertently received a block with a local anesthetic not scheduled in the protocol. No significant changes in vital signs were observed and no morbidity was observed or reported.

TABLE 1
Arm Group: Bupivacaine Block to One Side Only*

	Blocked side†	Unblocked side
AUC-PI‡	2.27 ± 1.50	7.34 ± 1.20
AUC-PR‡	20.23 ± 1.92	14.23 ± 1.66
AUC-VAS-PI§	124.78 ± 68.98	218.92 ± 43.26
AUC-VAS-PR‖	438.25 ± 74.27	307.75 ± 45.44

* Values are means ± SEM. Patient data: N = 9; age, 54.8 ± 5.6 years; weight, 64.7 ± 4.7 kg; height, 161.6 ± 3.6 cm; sex ratio, 8F:1M. Abbreviations used are: AUC-PI, area under curve against time pain intensity; AUC-PR, AUC pain relief; AUC-VAS-PI, AUC visual analogue pain intensity; AUC-VAS-PR, AUC visual analogue pain relief.

† Time to next analgesic (ranked minutes from time of block for each patient) 100, 105, 220, 250, 285, 1110, 1160, 1355, nil.

‡ $p < 0.005$, one-tailed Wilcoxon test.

§ $p < 0.05$, one-tailed Wilcoxon test.

‖ $p < 0.01$, one-tailed Wilcoxon test.

The results showed significantly better analgesia on the side that received the brachial plexus block with bupivacaine for the AUC-PI and AUC-PR indices ($p < 0.005$, one-tail Wilcoxon test), and for the AUC-VAS-PI and AUC-VAS-PR ($p < 0.05$ and $p < 0.01$, respectively, one-tail Wilcoxon test).

Five patients requested systemic analgesia within the study period (up to 450 minutes from the unilateral block); four patients did not require systemic analgesia for more than 1000 minutes after the block.

Ankle Group

The demographic data and results of the analgesic measures for the Ankle group are presented in Table 2. The side that received a bupivacaine ankle block had significantly better analgesia than the unblocked side for all four measures ($p < 0.005$ for AUC-PI, AUC-PR, AUC-VAS-PI, and AUC-VAS-PR, one-tail Wilcoxon test). No significant changes in vital signs were observed and no morbidity was observed or reported.

Seven patients requested systemic analgesia in the study period (up to 450 minutes from the unilateral block); the other three also required systemic analgesia within 1000 minutes.

BVL Group

The demographic data and results of the analgesic measures for the BVL group are presented in Table 3. There was no significant difference between the side blocked with bupivacaine and the side blocked with lidocaine for any of the four indices derived from the analgesic measurements. The times to next analgesic were significantly longer than those for the Ankle group in which only one side was blocked ($p = 0.05$, one-tail Mann-Whitney U-test).

TABLE 2
Ankle Group: Bupivacaine Block to One Side Only*

	Blocked side†	Unblocked side
AUC-PI	3.67 ± 1.41	10.28 ± 1.46
AUC-PR	18.08 ± 1.89	9.69 ± 1.89
AUC-VAS-PI	99.00 ± 38.89	308.35 ± 41.16
AUC-VAS-PR	477.65 ± 45.83	283.05 ± 42.40

* Values are means ± SEM. Patient data: N = 10; age, 48.0 ± 4.3 years; weight, 61.0 ± 3.8 kg; height, 163.5 ± 1.9 cm; sex ratio, 10F:0M. Abbreviations are defined in footnote to Table 1. In all cases, $p < 0.005$, one-tailed Wilcoxon test.

† Time to next analgesic (ranked minutes from time of block for each patient) 110, 160, 160, 270, 335, 375, 455, 460, 765, 950.

TABLE 3

BVL (Bupivacaine Versus Lidocaine) Group: Bupivacaine Ankle Block on One Side, Lignocaine Block on Other Side*

	Bupivacaine†	Lignocaine
AUC-PI	4.29 ± 1.37	6.21 ± 1.40
AUC-PR	18.85 ± 1.58	16.18 ± 1.69
AUC-VAS-PI	94.35 ± 42.84	122.98 ± 41.80
AUC-VAS-PR	472.83 ± 40.99	430.10 ± 47.26

* Values are means ± SEM. Patient data: N = 10; age, 37.0 ± 3.7 years; weight, 58.2 ± 1.9 kg; height, 165.2 ± 2.3 cm; sex ratio, 10F:0M. Abbreviations are defined in footnote tc Table 1. No significant difference on two-tailed Wilcoxon test for all groups.

† Time to next analgesic (ranked minutes from time of block for each patient) 220, 280, 370, 370, 435, 970, 1080, 1300, nil, nil.

Discussion

This paper presents one approach to a deceptively simple question: how may local anesthetics be compared for their analgesic effect in a relevant clinical context? This model, as described, may be valuable for evaluating duration and quality of analgesic action; a limitation is the inability to measure onset time.

The Arm and Ankle groups were designed with one treated and one untreated side to examine the sensitivity of the model. Both groups showed that the block with bupivacaine produced significantly greater analgesia than that provided by premedication and anesthesia for the unblocked side. This sensitivity was achieved even though the patients had normal systemic opiate administration for premedication and when required for postoperative pain. The Ankle group, however, showed significance of higher degree on the visual analogue measures.

The times to next analgesic for the Arm group showed that four of the nine patients required no analgesia until more than 1000 minutes after the block. This suggests that for some patients there is little advantage in the use of axillary brachial plexus block for postoperative pain relief unless the block provides analgesic duration well in excess of 1000 minutes. If morbidity results from a block, then the potential advantages, such as postoperative pain relief, are outweighed. For those patients whose pain relief from premedication and anesthetic was adequate for more than 1000 minutes, the block had doubtful value in view of the potential morbidity associated with performance of the block.

The significant differences between blocked and unblocked sides in the Ankle group showed that the block was effective. All the patients in the Ankle group had required further analgesia within 1000 minutes, unlike the Arm group. This suggests that for foot surgery a stronger case may be made for the use of local anesthetic blocks for postoperative pain relief than in arm surgery, both because of greater need for analgesia and because ankle blocks carry lower morbidity than axillary brachial plexus blocks.

The use of the bilateral model, providing within-patient comparison, also showed a difference in the analgesia provided by local anesthetic compared with parenteral opiate analgesia. Inadequate analgesia was treated with parenteral papaveretum. Although the opiate would affect the analgesic scores for both sides, the blocked side still had significantly greater measured analgesia than the unblocked side. The local anesthetic block was thus providing a quality of analgesia that was not matched by the parenteral opiate.

Ankle blocks were used for the next phase, blocks with a different local anesthetic on each side to allow comparison of the relative analgesic effects of the two agents. This was because they were technically easier to perform than brachial plexus blocks, had less risk of morbidity, and because the first phase had shown a greater need for blocks in foot surgery as opposed to arm surgery. The anesthetics chosen for the comparison were bupivacaine because of its accepted long duration of action (4) and lidocaine because of its more effective tissue penetration (5). Duration of action is an important factor in the choice of local anesthetic for blocks performed for postoperative pain relief. It should not be achieved at the expense of a high proportion of early failures in which the local anesthetic giving long duration analgesia has less effective tissue penetration. Tissue penetration may be especially important if landmarks are not always clear-cut, as with ankle blocks.

There were no significant differences in analgesic indices between bupivacaine and lidocaine over the 7.5-hour study period. Consequently, there was neither evidence to support the greater ability of lidocaine to penetrate tissues nor indication that the longer duration of bupivacaine compared with lidocaine is achieved with loss of analgesic quality in this early period.

Bilateral ankle blocks provide the sensitivity required to investigate subtle differences between suggested local analgesic procedures in realistic clinical procedures. One such difference is the addition of dextran to local analgesics.

ACKNOWLEDGMENTS

We wish to thank the surgeons and anesthetists at the Nuffield Orthopaedic Centre for allowing us to study their patients, and the

patients for taking part. We thank the anesthetic and recovery nursing staff for their assistance.

REFERENCES

1. Eriksson E. Brachial plexus block—axillary approach. In: Eriksson E, ed. Illustrated handbook in local anaesthesia. 2nd ed. London: Lloyd-Luke, 1979:82–4.
2. Lofstrom B. Nerve block at the ankle. In: Eriksson E, ed. Illustrated handbook in local anaesthesia. 2nd ed. London: Lloyd-Luke, 1979:114–5.
3. Wallenstein SL, Houde RW. The clinical evaluation of analgesic effectiveness. In: Ehrenpreis S, Neidle A, eds. Methods in narcotics research. New York: Marcel Dekker, 1975:127–45.
4. Atkinson RS, Rushman GB, Lee JA. A synopsis of anaesthesia. 8th ed. Bristol: Wright, 1977:357–8.
5. Atkinson RS, Rushman GB, Lee JA. A synopsis of anaesthesia. 8th ed. Bristol: Wright, 1977:355.

Use of Hydroxyethyl Starch in Hypovolemia and Shock

The effectiveness of 6% hydroxyethyl starch (hetastarch) solution for treatment of hypovolemia was evaluated in 46 critically ill patients. Thirty-two of the patients were studied retrospectively; cardiopulmonary variables were measured prospectively for the other 14 patients. Twenty-nine patients were in shock secondary to hypovolemia (13 patients), sepsis (13 patients), or myocardial infarction (three patients). Average hetastarch infusion volume was 829 and 842 ml, respectively, in prospectively and retrospectively studied patients, with maximum volumes of 2000 to 2500 ml infused over a 48-hour period. Approximately 30% of 24-hour fluid needs was supplied with colloids. Infusion of 500 ml of hetastarch in 14 retrospectively studied patients was associated with increases in pulmonary artery wedge pressure (PAW) from 9 ± 1.5 to 12 ± 2.1 mm Hg, cardiac index (CI) from 2.9 ± 0.2 to 3.5 ± 0.3 ($p < 0.05$) along with an increase in mean arterial pressure (MAP) from 87 to 99 mm Hg and reduction in arteriovenous O_2 difference [$C(a\text{-}v)_{O_2}$] from 4.9 to 4.2 ml/dl. Intrapulmonary shunt ($\dot{Q}sp/\dot{Q}t$) was similar (20% vs 21%) as were alveolar-arterial O_2 gradient [$P(A\text{-}a)_{O_2}$] (165 vs 158 torr), whereas O_2 consumption ($\dot{V}_{O_2}$) increased from 224 to 247 ml/min. Immediate survival was 90% in shock patients and 100% in nonshock patients, whereas hospital survival was 65.5% and 88%, respectively. The authors conclude that hetastarch is an effective fluid for resuscitation of hypovolemic patients. This synthetic colloid does not appear to affect pulmonary function adversely. (*Puri VK, Paidipaty B, White L. Hydroxyethyl starch for resuscitation of patients with hypovolemic shock. Crit Care Med 1981;9:833–7*)

ANESTH ANALG
1982;61:423-9

Antiarrhythmic and Hemodynamic Responses to Adenosine Triphosphate during Infusion of Epinephrine in Dogs Anesthetized with Halothane

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SOHN, Y. Z., HONG, J. C., AND KATZ, R. L.: Antiarrhythmic and hemodynamic responses to adenosine triphosphate during infusion of epinephrine in dogs anesthetized with halothane. Anesth Analg 1982;61:423–9.

The effects of adenosine triphosphate (ATP) on cardiovascular responses to epinephrine were evaluated in dogs anesthetized with halothane. The dose of epinephrine required to induce arrhythmias averaged 1.05 ± 0.52 μg/kg/min. The dose of ATP required to abolish these arrhythmias averaged 1.64 ± 0.67 mg/kg/min. ATP had not only an antiarrhythmic effect but also antagonized epinephrine-induced increases in heart rate, systemic vascular resistance, mean arterial blood pressure, and further increased cardiac index. ATP had, however, no significant effect on epinephrine-induced increases in myocardial contractility.

Key Words: METABOLISM: adenosine triphosphate; HEART: arrhythmias.

SINCE the original report of the effects of adenine compounds on the mammalian heart by Drury et al (1), other studies (2–6) of the cardiovascular effects of exogenously administered adenosine compounds have shown adenosine compounds to be potent coronary vasodilators and to have negative inotropic and chronotropic properties. Drury et al (1) also reported that adenine compounds arrested experimentally produced atrial fibrillation in mammalian heart experiments, but their experiments failed to show an antiarrhythmic action on ventricular arrhythmias. No further studies of antiarrhythmic effects of adenosine triphosphate (ATP) have been reported, but we recently observed that ATP demonstrated antiarrhythmic action on epinephrine-induced arrhythmias in the isolated rat ventricular papillary muscles (unpublished observation, 1980). The present study was designed to determine the antiarrhythmic effect of ATP on epinephrine-induced arrhythmias in dogs and to explore the possible modification by ATP of hemodynamic responses to epinephrine.

Methods and Materials

Eleven adult dogs of either sex, weighing approximately 22 kg each (18 to 28.5 kg), were anesthetized with intravenous sodium thiopental (20 mg/kg), intubated with cuffed orotracheal tubes, and placed in the supine position.

Ventilation was controlled with a Harvard respirator delivering 1.0 vol% halothane in air. An initial dose of 0.3 mg/kg of *d*-tubocurarine was given and was followed by 1.0 mg every hour.

Tidal volume and frequency of respiration were set to maintain the ET_{CO_2} at approximately 5%. This was monitored with a CO_2 gas analyzer (Beckman medical gas analyzer, LB-2). Esophageal temperature was monitored with the thermistor thermometer (Dupaco 54000) and maintained with a heating lamp between 35 and 37.5°C throughout the study.

A continuous lead II electrocardiogram (ECG) monitored heart rate and rhythm. Two peripheral intravenous catheters were inserted for fluid maintenance and administration of experimental drugs.

AP was monitored via a Teflon catheter inserted through a femoral artery. This catheter was also used for sampling of blood for measurement of blood gas tensions, Ht, and serum levels of electrolytes, lactate,

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Supported by intramural fund, University of California at Los Angeles, UCLA Foundation, and Medrec Inc.
Received from the Department of Anesthesiology, University of California at Los Angeles, School of Medicine, 10833 LeConte Avenue, Los Angeles, California 90024. Accepted for publication January 11, 1982.
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and ionized calcium. A flow-directed balloon-tipped (Swan-Ganz) catheter was advanced via the right external jugular vein into the pulmonary artery for measurement of PAP, PCWP, RAP, and cardiac output using a thermodilution technique (cardiac output computer, Edwards Laboratories 9520A).

AP, PAP, and RAP were measured with Hewlett-Packard Quartz transducers (1290A). A Mikro-tip catheter pressure transducer (PC-350) was also placed via the left carotid artery into the left ventricle for measurement of LVSP and its first derivative (LV dP/dt) which was divided by the instantaneous developed pressure in the ventricle to use as an indicator of myocardial contractility (LV dP/dt/LVSP). MAP, MPAP, CI, SVI, LVSWI, SVR, and PVR were calculated with a programmable calculator (Texas Instruments, PC-100C). All monitors were connected to the HP 8-channel recorder (7758B) and recorded at a paper speed of 5×10^{-1} mm/sec until the ECG showed premature ventricular contractions (PVCs) at which the paper speed was increased to 10 and 50 mm/sec. The ECG output from the Hewlett-Packard recorder was connected to an oscilloscope (Datascope 850) to detect changes in cardiac rhythm. Intravenous infusion of 5% dextrose in lactated Ringer's solution at 100 ml/hr was continued for the duration of study. All dogs were allowed to stabilize for 1 hour following administration of halothane and surgical procedures. Blood loss during surgical procedures was minimal (less than 10 ml).

Arterial blood samples were drawn from the femoral arterial catheter, collected in heparinized syringes, and immediately placed on ice for determinations of control data before administration of drugs and again 30 minutes after drugs were discontinued.

Two other arterial blood samples were drawn as soon as four or more PVCs appeared within 15 seconds during epinephrine infusion and as soon as PVCs disappeared with adenosine triphosphate (ATP). Pa_{O_2}, Pa_{CO_2}, pHa, BE, Ht, and serum levels of sodium (Na^+), potassium (K^+), chloride (Cl^-), bicarbonate (HCO_3^-), ionized calcium (Ca^{2+}), and lactate were measured in our laboratory.

Epinephrine (Elkins-Sinn, Inc.) and ATP (Sigma, from equine muscle disodium salt) were prepared in normal saline to 30 μg/ml and 40 mg/ml, respectively. These two solutions were connected to the one of the intravenous infusion tube via a "T" connector just proximal to the inserted intravenous catheter and rates of infusion were controlled by Holter pumps (Extracorporeal, 907) with size "D" pump chamber which could range from 0.5 to 2.5 μg/kg/min of epinephrine and 1 to 3 mg/kg/min of ATP. Hemodynamic and laboratory data obtained in anesthetized dogs were used as controls.

Study of Antiarrhythmic Effect of ATP

After a control ECG (C_1, before epinephrine or ATP infusion was begun) was recorded, a continuous infusion of epinephrine was begun at the rate of 0.5 μg/kg/min and increased in 0.5-μg/kg/min increments until arrhythmias were induced. Each rate of infusion was continued for 3 minutes before the rate was increased. Four or more premature ventricular contractions (PVCs) within 15 seconds were considered successfully induced arrhythmias in this study. Once the arrhythmias were induced the epinephrine infusion was continued and ATP infusion was begun at the rate of 1 mg/kg/min and increased in 1-mg/kg/min increments every 3 minutes until PVCs disappeared. As soon as PVCs disappeared, the infusions of epinephrine and ATP were both discontinued and the dogs were allowed to stabilize for 20 minutes before recording another control ECG (C_2, after drugs were discontinued).

ABBREVIATIONS

HR	heart rate (beat/min)
CI	cardiac index (L/min/m^2)
SVI	stroke volume index (ml/beat/m^2)
AP	arterial pressure (torr)
MAP	mean arterial pressure (torr)
SVR	systemic vascular resistance (dyne/sec/cm^5)
LVSWI	left ventricular stroke work index (g m/m^2/beat)
LVSP	left ventricular systolic pressure (torr)
LV dP/dt	first derivative of the left ventricular pressure (torr/sec)
LV dP/dt/LVSP	as indicator for myocardial contractility
PAP	pulmonary arterial pressure (torr)
MPAP	mean pulmonary arterial pressure (torr)
PCWP	pulmonary capillary wedge pressure (torr)
RAP	right atrial pressure (torr)
PVR	pulmonary vascular resistance (dyne/sec/cm^5)
pHa	pH of arterial blood
Pa_{O_2}	partial pressure of arterial oxygen (torr)
Pa_{CO_2}	partial pressure of arterial carbon dioxide (torr)
BE	base excess of arterial blood
Ht	hematocrit (%)
ET_{CO_2}	end-tidal CO_2 (%)

For evaluation of dose-related responses to ATP and epinephrine, epinephrine infusion was begun at the rate of 0.5 μg/kg/min for 3 minutes and was then increased in 0.5-μg/kg/min increments every 3 minutes until four or more PVCs occurred within 15 seconds. At the time arrhythmias occurred, ATP infusion was begun at a rate of 1 mg/kg/min for 3 minutes and the rate then increased every 3 minutes in 1-mg/kg/min increments until PVCs disappeared (during this time the epinephrine infusion was continued). As soon as PVCs disappeared, the rate of epinephrine infusion was increased to the next higher rate and continued for 3 minutes or until PVCs recurred (during this time the ATP infusion was contin-

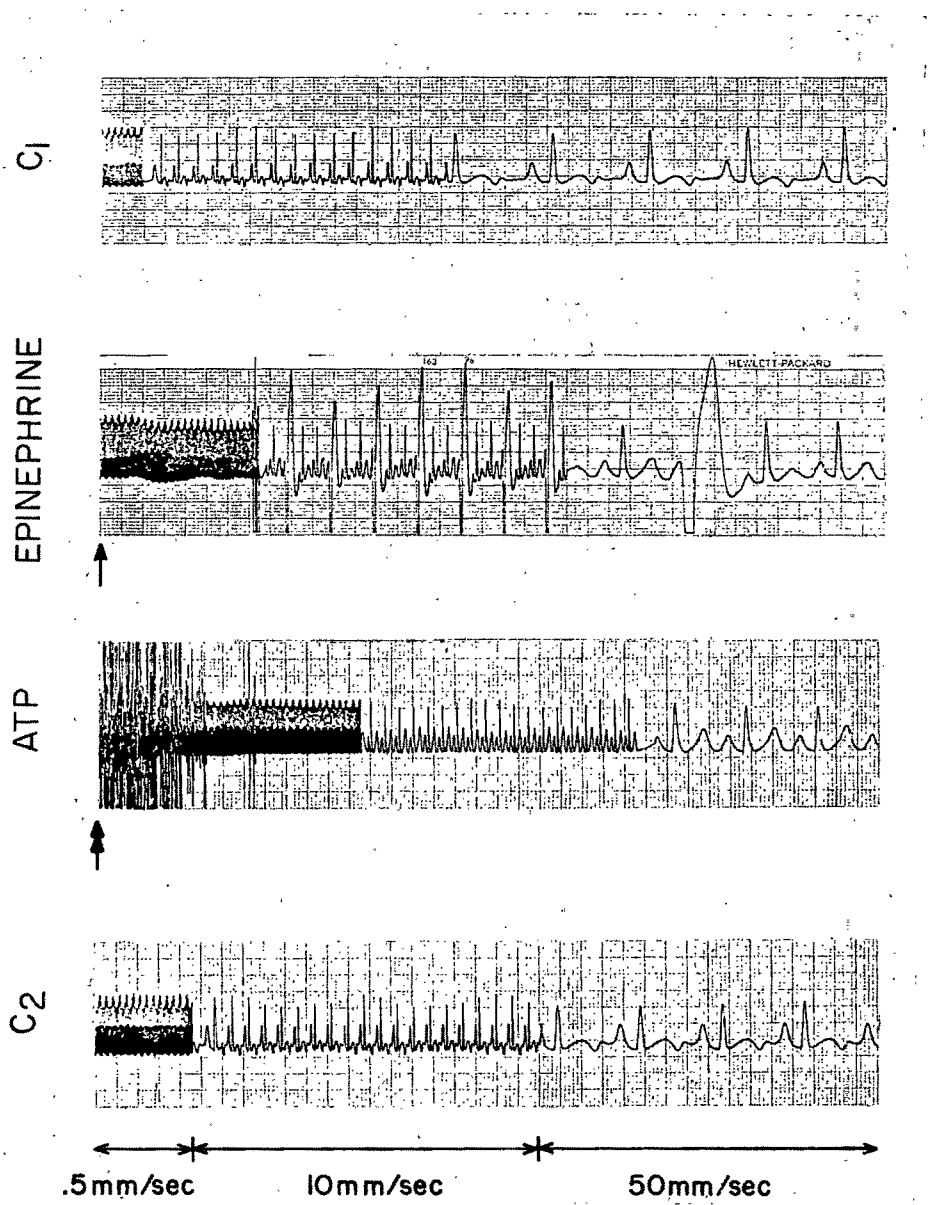


FIG 1. Electrocardiogram (ECG) changes in an anesthetized dog, showing that adenosine triphosphate (ATP) reverses epinephrine-induced arrhythmias. Epinephrine-infusion began at single arrow (0.5 μg/kg/min IV) and ATP infusion began at double arrow (1 mg/kg/min IV). Panels, top to bottom; C_1, control ECG tracing before any drug was given; epinephrine, ECG tracing during epinephrine-infusion; ATP, ECG tracing during ATP infusion with continuous epinephrine infusion; C_2, control ECG tracing 20 minutes after epinephrine and ATP infusions were discontinued. Each ECG tracing was recorded at three different paper speeds (0.5, 10, and 50 mm/sec).

ued). These step-up sequences were continued until study of the epinephrine-ATP interaction was completed

Study of Hemodynamic Effects of ATP during Epinephrine Infusion

The hemodynamic changes (HR, AP, LVSP, LV dP/dt, PAP, RAP, and ET_{CO_2}) were recorded continuously, and MAP, MPAP, CI, SVI, SVR, LVSWI, PCWP, and LV dP/dt/LVSP were measured and calculated at the time arrhythmias (PVCs) occurred with epinephrine and at the time PVCs disappeared with ATP during the continuous infusion of epinephrine. All these data were recorded and blood samples were drawn at the same time ECGs were recorded for control-1 (pre-experiment), control-2 (postexperiment), epinephrine, and epinephrine plus ATP.

Statistical methods. Data were analyzed using Student's paired *t*-test. Linear regression analysis was done by using Hewlett-Packard calculator (9805A) and calculator plotter (9862A); p values ≤ 0.05 were considered statistically significant.

Results

Antiarrhythmic Effects of ATP

A typical antiarrhythmic effect of ATP is shown in Fig 1. It shows that infusion of epinephrine (0.5 μg/kg/min) induced arrhythmias (PVCs) in a dog anesthetized with halothane and that ATP (1 mg/kg/min) had an antiarrhythmic effect. It took approximately 90 seconds for ATP to abolish the arrhythmias. In these experiments the average dose of epinephrine required to meet our criteria of arrhythmias (four or more premature ventricular beats within 15 seconds) was 1.05 ± 0.52 μg/kg/min and the average dose of ATP required to abolish these arrhythmias was 1.64 ± 0.67 mg/kg/min. The dose relationships between epinephrine and ATP (Fig 2) were significantly correlated ($r = 0.83$). The higher the dose of epinephrine used to induce arrhythmias, the more ATP was required to restore these arrhythmias to normal sinus rhythms. When the dose of epinephrine was increased by 0.5 μg/kg/min to induce arrhythmias, it was necessary to increase the dose of ATP by 1 mg/kg/min.

Hemodynamic Effects of ATP during Epinephrine Infusion

In Table 1 are shown the hemodynamic data (mean ± SD) from 11 dogs including control data, data at the time arrhythmias occurred with infusion of epinephrine, and data at the time arrhythmias disappeared with ATP despite the continuous infusion of epinephrine. When ATP was given during infusion of epinephrine there were statistically significant reductions from the effects of epinephrine in MAP (22.00% ± 10.77%), SVR (46.64% ± 17.55%), LVSP (17.00% ± 9.25%), MPAP (28.64% ± 19.22%), PCWP (57.00% ± 9.73%), and RAP (21.82% ± 22.19%), whereas ATP increased epinephrine-induced changes in CI, SVI, LVSWI, and PVR by 56.55% ± 38.82%, 86.27% ± 61.20%, 64.64% ± 75.42%, and 87.00% ± 134.73%, respectively. However, ATP had no significant effects on epinephrine-induced changes in HR, LV dP/dt, and LV dP/dt/LVSP. A typical experiment showing the changes in hemodynamic measurements is shown in Fig 3. Laboratory data shown in Table 2, indicate that there are significant reductions from the effects of epinephrine in pHa, BE, HCO_3^-, and K^+, whereas Pa_{CO_2} and Ht are significantly increased. However, there are no significant changes in levels of Pa_{O_2}, lactate, ET_{CO_2}, Na^+, Cl^-, and Ca^{2+} (lactate, Na^+, Cl^-, and Ca^{2+} data are not shown because no changes were seen).

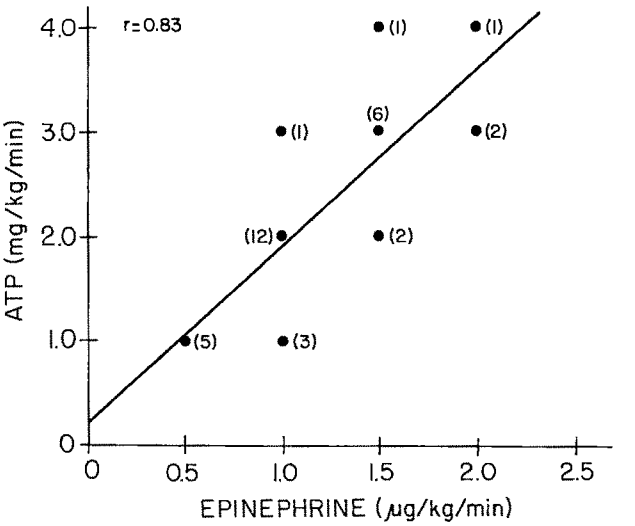


FIG 2. Relationship between minimum antiarrhythmic doses of ATP and various arrhythmic doses of epinephrine. Numbers in parentheses indicate number of experiments; *r*, linear regression.

Discussion

Adenosine triphosphate (ATP) demonstrated an antiarrhythmic action against epinephrine-induced arrhythmias in dogs anesthetized with 1.0 vol% halothane in air. In our study, arrhythmic doses of epinephrine, 1.05 ± 0.52 μg/kg/min, needed to meet our criteria of arrhythmias were lower than those reported

TABLE 1

Hemodynamic Data before Infusion of Epinephrine (Control), at Time Arrhythmias Occurred with Infusion of Epinephrine (Epinephrine), and at Time Arrhythmias Disappeared with ATP during Continuous Infusion of Epinephrine (Epinephrine + ATP)*

	Control	*p* value†	Epinephrine	*p* value‡	Epinephrine + ATP
HR	124 ± 24	≤0.05	181 ± 43	NS	156 ± 41
CI	3.98 ± 1.28	NS	4.09 ± 0.87	≤0.05	6.15 ± 1.12
SVI	33 ± 11	≤0.05	24 ± 7	≤0.05	41 ± 10
MAP	100 ± 14	≤0.05	166 ± 16	≤0.05	129 ± 18
SVR	1979 ± 467	≤0.05	3185 ± 872	≤0.05	1631 ± 466
LVSWI	41 ± 16	NS	44 ± 15	≤0.05	65 ± 18
LV dP/dt	2640 ± 624	≤0.05	4470 ± 824	NS	4290 ± 819
LVSP	121 ± 19	≤0.05	193 ± 30	≤0.05	159 ± 17
LV dP/dt/LVSP	21.81 ± 3.66	NS	23.73 ± 6.22	NS	27.67 ± 8.26
MPAP	13 ± 3	≤0.05	31 ± 6	≤0.05	22 ± 6
PCWP	8 ± 2	≤0.05	31 ± 7	≤0.05	13 ± 2
RAP	6 ± 2	≤0.05	11 ± 3	≤0.05	8 ± 3
PVR	104 ± 64	≤0.05	60 ± 70	≤0.05	119 ± 76

* Values are means ± SD; N = 11. NS, no significant difference.

† Between control and epinephrine groups.

‡ Between epinephrine and epinephrine + ATP groups.

by others (7–9). This difference may be due to differences in anesthetic techniques, blood gas tensions, surgical techniques, and criteria of arrhythmia. In our experiments 1.0 vol% of halothane in air was used to maintain anesthesia. Control Pa_{O_2} during ventilation with air was an average of 98 torr. Respiration was controlled to keep end-tidal CO_2 at approximately 35 torr during the control period. Sodium bicarbonate was not given because it may affect the initiation or cessation of arrhythmias. The onset of action of ATP was abrupt and the duration of action was brief when the ATP infusion was stopped. However, in this study, it took approximately 90 seconds to restore the epinephrine-induced arrhythmias to sinus rhythm, possibly because this amount of time was required to achieve a concentration of ATP necessary to counteract the effect of epinephrine. As seen in Fig 2 the higher the dose of epinephrine used to induce arrhythmias, the more ATP was needed (1 mg/kg of ATP for each 0.5 μg/kg of epinephrine). The dose relationship of ATP and epinephrine was significantly correlated.

Catecholamines precipitate arrhythmias by binding with beta-1-adrenergic receptors, activating adenylate cyclase and then increasing cyclic AMP. Although not yet clear, the possible mechanism of antiarrhythmic action of ATP may, in part, be due to inhibitory action of ATP on the epinephrine-induced activation of adenylate cyclase. Schrader et al. (10) reported that in guinea pig ventricles adenosine inhibited catecholamine-induced stimulation of cardiac adenylate cyclase and this may account for the antiarrhythmic effect we observed. As reported by others (11), the antiarrhythmic effect of ATP apparently does not directly involve the beta-1-adrenergic receptors. Rather, these studies indicate that ATP has a direct stabilizing effect on cardiac cell membranes. Many of the epinephrine-induced hemodynamic effects were modified at the time ATP abolished the arrhythmias. MAP along with SVR, LVSP, MPAP, PCWP, and RAP decreased significantly whereas CI along with SVI, LVSWI, and PVR increased significantly. However, HR, LV dP/dt, and LV dP/dt/LVSP were not significantly affected by ATP during epinephrine infusion. These findings suggest that most changes in hemodynamics produced by ATP during epinephrine infusions may be primarily due to ATP-induced changes in vascular resistance rather than due to changes in myocardial contractility. This supports the concept that ATP is not only a strong vasodilator but that it also inhibits the action of epinephrine on vascular smooth muscles (12).

ATP is known to have a negative chronotropic action. The mechanism of this action is not entirely clear but may be due to indirect (vagal) action (4), to direct action on the SA node (3), to direct action of ATP on cardiac muscle to inhibit the noradrenaline release (4), to an effect of ATP on the re-uptake of Ca^{2+} by sarcoplasmic reticulum (11, 13), or to any combination of the above. In this study ATP did not significantly decrease the increase in HR produced by epinephrine. However, the mean HR of 11 experiments was reduced from 181 to 156 beats per minute. The reasons for these failures to affect epinephrine-

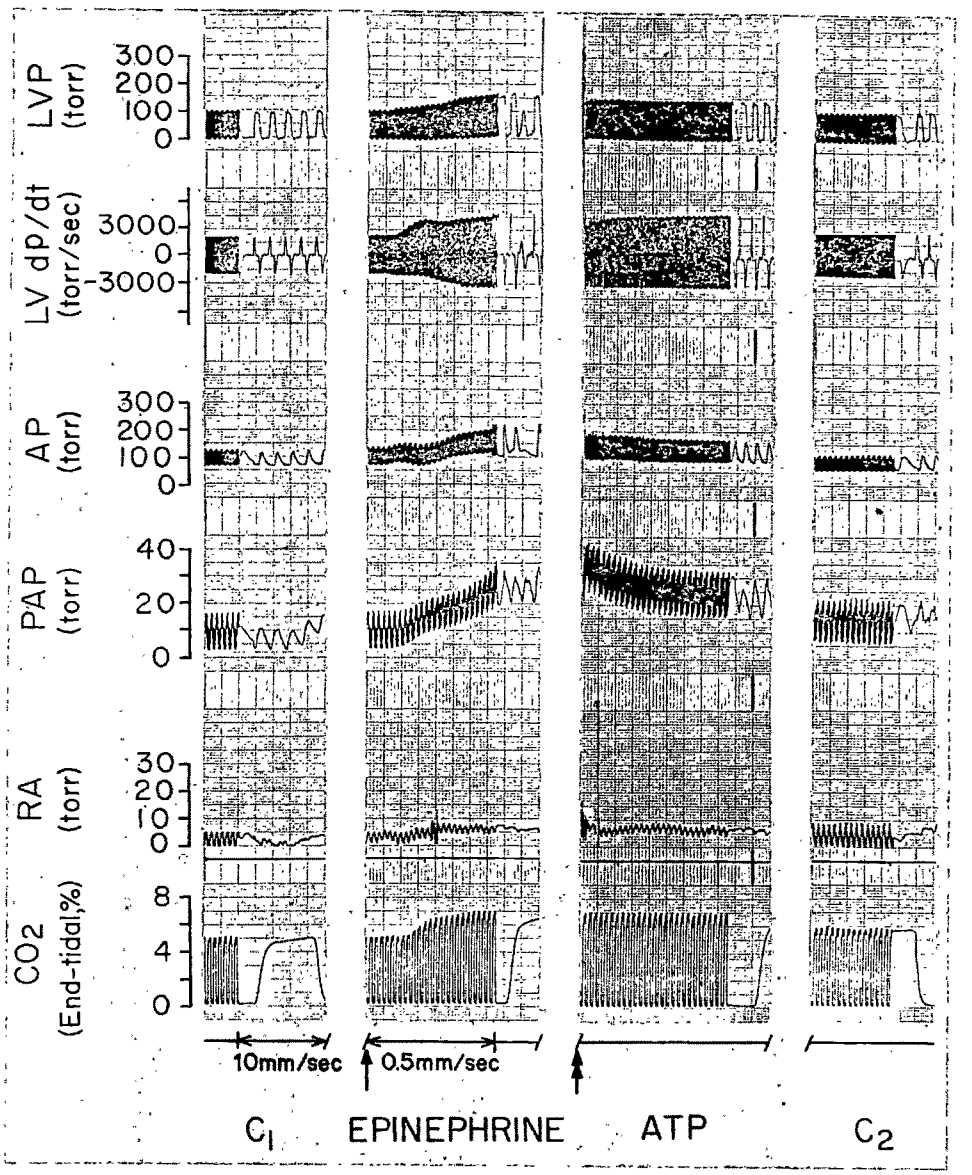


FIG 3. Changes in cardiovascular functions produced by ATP when administered during infusion of epinephrine. Epinephrine infusion was begun at single arrow (0.5 μg/kg/min IV) and ATP infusion was begun at double arrow (1 mg/kg/min IV) along with continuous epinephrine infusion. C_1, control before epinephrine and ATP were given; C_2, control 20 minutes after epinephrine and ATP were discontinued. All tracings were recorded at two different paper speeds (0.5 and 10 mm/sec).

induced increase in HR may be related to the fact that we recorded the ECG as soon as ATP stopped the arrhythmias, which took approximately 90 seconds, or to the fact that the infusion of epinephrine was continued together with ATP infusion.

pH and BE together with HCO_3^- decreased significantly when ATP was added to the infusion of epinephrine but Pa_{CO_2} increased further. ATP had, however, no effect on Pa_{O_2} during epinephrine infusion.

Levels of K^+ significantly decreased following the addition of ATP to epinephrine, Ht was significantly increased, and there were no significant changes in levels of lactate, Na^+, Cl^-, and Ca^{2+}. It is thought that these changes are not produced by ATP because: (*a*) ATP-infusion was begun during the continuous infusion of epinephrine, and (*b*) time interval between the two blood samples, one at the time arrhythmias began with epinephrine and one at the time arrhythmias ceased with ATP, is short, approximately 3 minutes. These changes are mostly produced by epinephrine.

Decrease in Pa_{O_2}, increase in Pa_{CO_2}, increase in

TABLE 2

Laboratory Data before Infusion of Epinephrine (Control), at Time Arrhythmias Occurred with Infusion of Epinephrine (Epinephrine), and at Time Arrhythmias Disappeared with ATP during Continuous Infusion of Epinephrine (Epinephrine + ATP)*

	Control	p value†	Epinephrine	p value‡	Epinephrine + ATP
pHa	7.30 ± 0.07	NS	7.29 ± 0.04	≤0.05	7.25 ± 0.03
Pa_{O_2}	98 ± 4	≤0.05	85 ± 12	NS	85 ± 11
Pa_{CO_2}	39 ± 7	≤0.05	43 ± 7	≤0.05	45 ± 7
BE	−7.5 ± 2.8	≤0.05	−5.8 ± 2.1	≤0.05	−7.1 ± 2.1
HCO_3^-	21 ± 2	NS	23 ± 3	≤0.05	21 ± 3
ET_{CO_2}	5.15 ± 0.78	≤0.05	5.99 ± 0.69	≤0.05	6.18 ± 0.69
K^+	3.6 ± 0.3	≤0.05	4.9 ± 0.7	≤0.05	4.3 ± 0.7
Ht	39.5 ± 3.3	≤0.05	47.8 ± 3.5	≤0.05	49.0 ± 3.5

* Values are means ± SD. NS, no significant difference.

† Between control and epinephrine groups.

‡ Between epinephrine and epinephrine + ATP groups.

serum K^+ levels followed by decrease and increase in Ht were observed during epinephrine-infusion as described by others (14).

In summary, ATP protected against arrhythmias induced by epinephrine and antagonized some of the cardiovascular effects of epinephrine in halothane-anesthetized dogs. There is a good correlation between protective doses of ATP and arrhythmogenic doses of epinephrine. The antiarrhythmic action of ATP may be due to inhibition of myocardial effects of epinephrine but may not be mediated at the same site where the arrhythmogenic action of epinephrine is exerted. Further complete studies of the mechanism of antiarrhythmic action of ATP, including blood levels of catecholamines before and during ATP infusion and metabolic changes produced by ATP, are indicated.

REFERENCES

1. Drury AN, Szent-Györgyi A. The physiological activity of adenine compounds with especial reference to their action upon the mammalian heart. J Physiol 1929;68:213–37.
2. Rowe GG, Afonso S, Gurtner HP, et al. The systemic and coronary hemodynamic effects of adenosine triphosphate and adenosine. Am Heart J 1962;64:228–34.
3. James TN. The chronotropic action of ATP and related compounds studied by direct perfusion of the sinus node. J Pharmacol Exp Ther 1965;149:233–47.
4. Green HN, Stoner HB, eds. Biological actions of the adenine nucleotides. London: H K Lewis and Co, Ltd, 1950:23–103.
5. Emmelin N, Feldberg W. Systemic effects of adenosine triphosphate. Br J Pharmacol 1978;3:273–84.
6. Hollander PB, Webb JL. Effects of adenine nucleotides on the contractility and membrane potentials of rat atrium. Circ Res 1957;5:349–53.
7. Pace NL, Ohmura A, Wong KC. Epinephrine-induced arrhythmias: effect of exogenous prostaglandins and prostaglandin synthesis inhibition during halothane-O_2 anesthesia in the dog. Anesth Analag 1979;58:401–4.
8. Joas TA, Steven WC. Comparison of the arrhythmic doses of epinephrine during Forane, halothane and fluroxene anesthesia in dogs. Anesthesiology 1971;35:48–53.
9. Zink J, Sasyniuk BI, Dresel PE. Halothane-epinephrine induced cardiac arrhythmia and the role of heart rate. Anesthesiology 1975;43:548–55.
10. Schrader J, Baumann G, Gerlach E. Adenosine as inhibitor of myocardial effects of catecholamine. Pfluegers Arch 1977; 365:29–35.
11. Yatani A, Goto M, Tsuda Y. Nature of catecholamine like actions of ATP and other energy rich nucleotides on the bullfrog atrial muscle. Jpn J Physiol 1978;28:47–61.
12. Hedqvist P, Fredholm BB. Inhibitory effect of adenosine on adrenergic neuroeffector transmission in the rabbit heart. Acta Physiol Scand 1979;105:120–2.
13. Schrader J, Rubio R, Berne RM. Inhibition of slow action potentials of guinea pig atrial muscle by adenosine: a possible effect on Ca^{++} influx. J Mol Cell Cardiol 1975;7:427–33.
14. Innes IR, Nickerson M. Norepinephrine, epinephrine and the sympathomimetic amines. In: Goodman LS, Gilman A, eds. The pharmacological basis of therapeutics. New York: Macmillan, 1975:485–513.

ANESTH ANALG
1982;61:430-3

Intracranial Hypertension during Surgery for Supratentorial Tumor: Correlation with Preoperative Computed Tomography Scans

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BEDFORD, R. F., MORRIS, L., AND JANE, J. A.: Intracranial hypertension during surgery for supratentorial tumor: correlation with preoperative computed tomography scans. Anesth Analg 1982;61:430-3.

To test the hypothesis that preoperative head computed tomography scans could be used to predict the likelihood that a patient with a supratentorial brain tumor would develop intracranial hypertension during surgery before the cranium was opened, intraoperative intracranial pressure and blood pressure records of 60 patients undergoing craniotomy were compared with the appearance of their preoperative computed tomography scans. The scans were interpreted by a neuroradiologist who was unaware of the clinical events in each case. A positive correlation was found between the amount of preoperative brain edema observed surrounding tumors (on an arbitrary 0 to 3+ scale) and subsequent increases in intracranial pressure greater than base line values. No such correlation could be found with regard to tumor size, shift of midline structures, or effacement of the lateral ventricles. When preoperative brain edema seen on computed tomography scan was taken into consideration, increases in intracranial pressure during craniotomy also correlated with simultaneous increases in blood pressure. It is concluded that patients with large amounts of preoperative brain edema surrounding supratentorial tumors should be considered at risk for developing intraoperative intracranial hypertension and may benefit from preoperative insertion of an intracranial pressure monitor before general anesthesia is induced.

Key Words: BRAIN: intracranial pressure; EQUIPMENT: computed tomography; BLOOD PRESSURE.

INTRACRANIAL hypertension may occur in patients with supratentorial brain tumors, either during induction of anesthesia and endotracheal intubation, or during the early stages of craniotomy before the dura is opened (1). Although placement of an intracranial pressure (ICP) monitor in these patients before anesthetic induction can help the anesthetist to optimize control of ICP before the cranium is opened, this procedure requires additional operating room time, added risk, and at least some discomfort to the patients who may or may not be cooperative. The present study was undertaken to test the hypothesis that preoperative examination of computed tomography (CT) scans could help to identify those patients most likely to benefit from ICP monitoring during the period from the induction of anesthesia until the cranium is opened.

Methods

The protocol for this study was approved by the local human studies committee and informed consent was obtained from each patient and his nearest relative. The subjects were 60 patients scheduled for elective craniotomy for supratentorial tumors. All were receiving oral dexamethasone, 80 mg/day, before surgery. Using local anesthesia, a subarachnoid screw and radial arterial catheter were placed, and ICP and blood pressure levels were continuously transduced and recorded. Intracranial compliance (delta volume/delta pressure) was estimated from the change in ICP induced by a 1-ml bolus injection of mock cerebrospinal fluid through the subarachnoid screw. Anesthesia was induced using thiopental, 3 mg/kg; morphine, 0.3 mg/kg; pancuronium, 0.1 mg/kg; and nitrous oxide, 70% in oxygen. Ventilation was controlled mechanically, maintaining a constant end-

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Received from the Departments of Anesthesiology, Neurological Survey, and Radiology, University of Virginia Medical Center, Charlottesville, Virginia. Accepted for publication January 13, 1982. Presented at the Annual Meeting of the Society of Neurosurgical Anesthesia and Neurological Supportive Care, 1981.
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tidal CO_2 fraction (Beckman LB-2), and arterial blood gas tension levels were obtained to verify adequacy of ventilation. Despite apparently optimal anesthetic conditions [$Paco_2$ = 31 ± 3 (SD) torr and ICP = 11 ± 4 (SD) torr], in 31 of the 60 patients, marked increases in ICP, usually associated with endotracheal intubation, application of a pin head-holder, or surgical incision [mean duration of increased ICP = 2.9 ± 1.7 (SD) min], were observed. Whenever ICP increased above 25 torr, thiopental, 3 mg/kg IV, was given to return ICP to normal values.

Each patient's CT scan, which had been performed within the week before surgery, was evaluated with regard to maximum tumor diameter (cm), shift of midline structures (mm), diminished attenuation indicating brain edema (on an arbitrary scale of 0 to 3+, Figs 1 to 3), and ventricular effacement. The radiologist evaluating the scan was unaware of the patient's clinical course. Statistical comparisons were performed using Student's *t*-test for nonpaired data and Fisher's exact test; $p < 0.05$ was regarded as statistically significant.

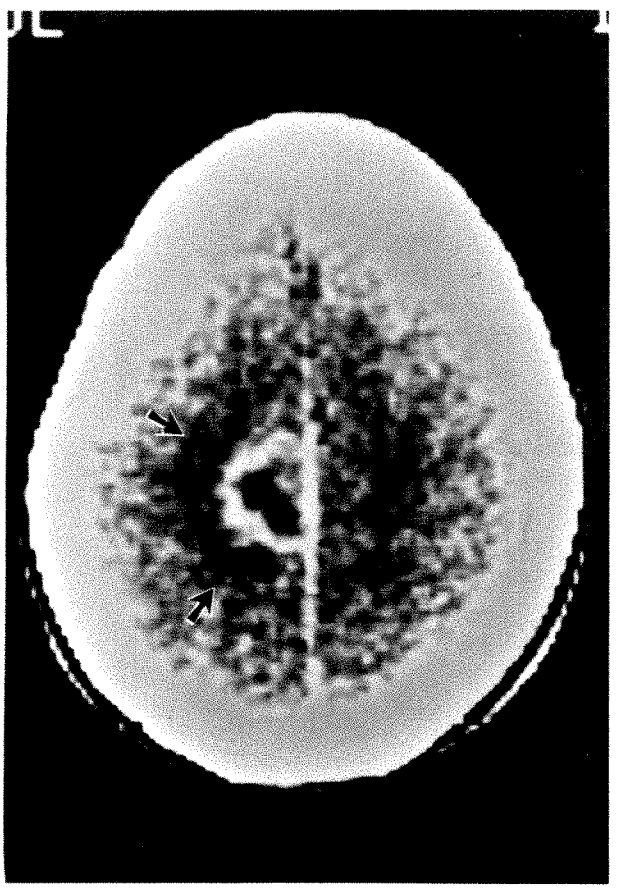


FIG 1. Computed tomographic (CT) head scan showing cystic parasaggital glioma with small (1+) rim of edema appearing as circumscribed dark band of diminished attenuation (arrow) around enhancing rim of tumor.

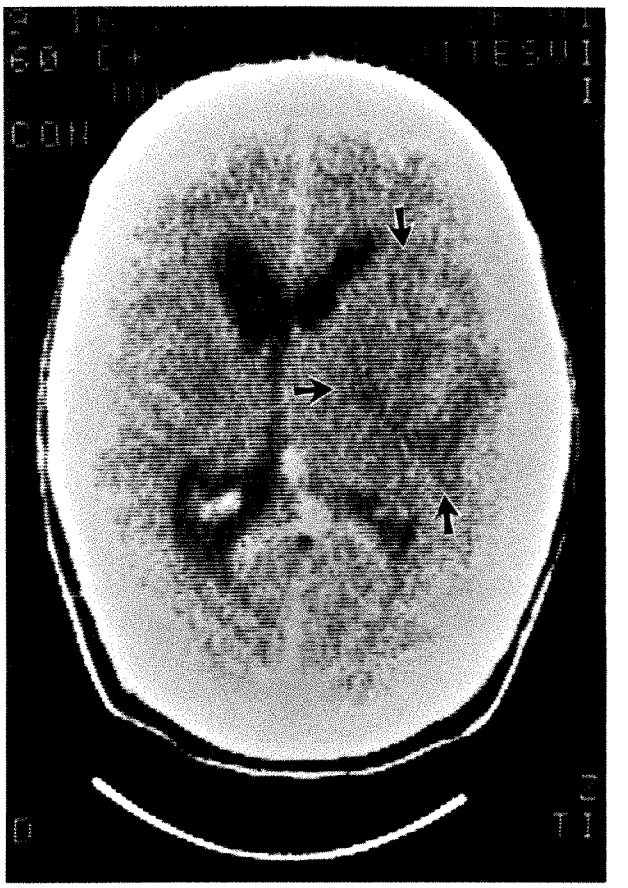


FIG 2. Frontoparietal glioma with wider band (arrows) of edema (2+) causing effacement of lateral ventricles and 5-mm right-to-left shift of midline structures.

Results

Among the factors that could be evaluated from the preoperative head CT scans, the amount of brain edema visualized adjacent to the patients' supratentorial tumors could be most closely correlated with the development of elevations in intraoperative ICP (Fig 4). Tumor size, ventricular effacement, and shift of midline structures were not reliable predictors of intracranial hypertension. However, patients with small tumors (<3 cm diameter) and no evidence of edema, midline shift, or ventricular effacement were never found to develop elevated ICP.

When patients were divided into groups according to the amount of brain edema on CT scan (Table), we observed progressively lower intracranial compliance and progressively greater shift of midline structures as the amount of edema increased. Furthermore, eight

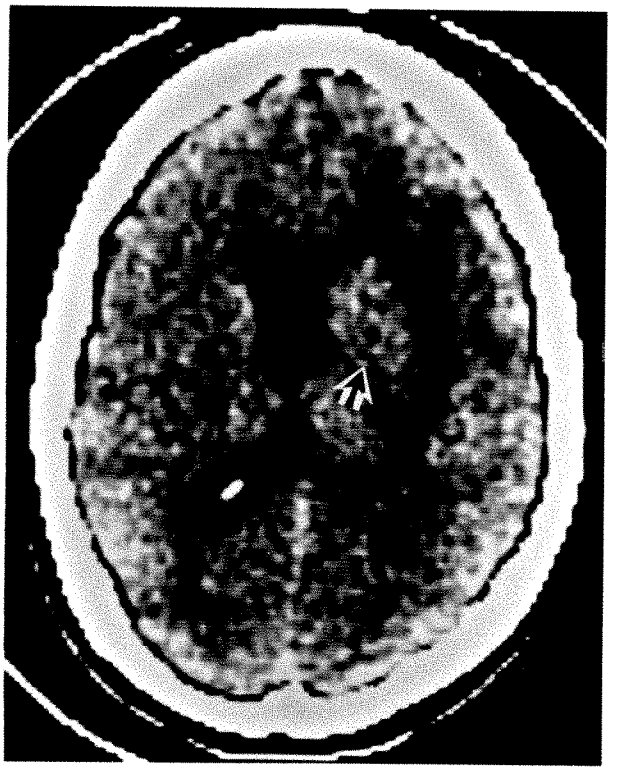


FIG 3. Enhancing glioma (arrow) with extensive edema (3+) extending through entire right hemisphere.

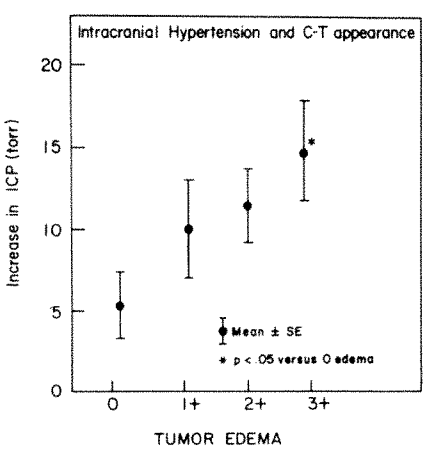


FIG 4. Patients with minimal preoperative edema around their brain tumors sustained relatively small increases in ICP during general anesthesia. In contrast, those with more edema developed progressively greater increases in ICP before cranium was opened.

of the 21 patients with 3+ brain edema required thiopental therapy for rapid reduction of ICP > 25 torr, whereas only one patient in each of the other groups with lesser degrees of edema required such intervention ($p < 0.05$).

Increases in ICP could also be correlated with increases in blood pressure in response to such noxious stimuli as endotracheal intubation and surgical incision when the amount of brain edema surrounding supratentorial tumors was taken into consideration (Fig 5). Larger amounts of edema apparently resulted in impaired autoregulation and greater increases in ICP as blood pressure increased above the values measured before surgery while patients were awake.

Discussion

Previous attempts to correlate CT scan appearance with changes in ICP in patients with head trauma have not been successful except to identify patients with normal brains who were not at risk for developing intracranial hypertension (2). Unlike the global nature of many closed head injuries, however, focal lesions such as supratentorial brain tumors produce a circumscribed mass lesion, often with a halo area of

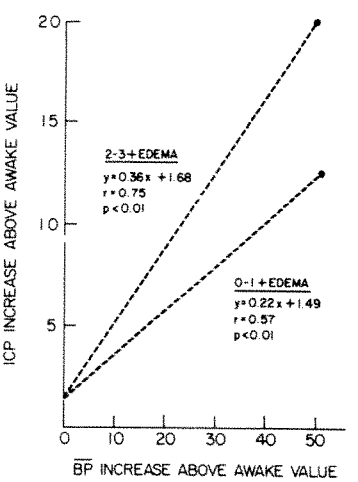


FIG 5. Increases in ICP greater than awake values correlated with increases in blood pressure greater than awake values when patients were grouped according to relatively large (2 to 3+) or small (0 to 1+) amounts of edema seen on preoperative CT scan.

TABLE

Brain Edema*

	0	1+	2+	3+
No. of patients	12	12	15	21
Delta volume (ml)/delta ICP (torr)	0.63 ± 0.16†	0.42 ± 0.8	0.35 ± 0.6	0.25 ± 0.5
Midline shift (mm)	1.5 ± 0.9†	2.0 ± 1.4†	5.4 ± 1.2	8.5 ± 2.7

* Values are means ± SE.

† $p < 0.05$ vs 3+ edema group.

cerebral edema which can be readily identified on preoperative CT scan. A progressively widening band of edema indicates loss of normal intracranial compliance and also probable impairment of cerebrovascular autoregulation, even though many of these patients may be surprisingly alert and cooperative and have normal ICP before surgery.

The findings of this study indicate that the appearance of the preoperative CT scan can identify those patients with supratentorial tumors who are most likely to develop intracranial hypertension before the cranium is opened. As these increases in ICP are readily amenable to treatment once the diagnosis is made, these are the patients most likely to benefit from intraoperative ICP monitoring. If ICP monitoring is not feasible, then the most effective anesthetic technique for preventing occult intracranial hypertension before the cranium is opened appears to include the maintenance of normal arterial pressure with appropriate doses of barbiturate given intravenously just before painful stimulation occurs.

In conclusion, we believe that proper preanesthetic evaluation of patients with supratentorial tumors should include not only a preoperative interview and physical examination but also an evaluation of the CT scan with particular attention paid to the amount of brain edema observed surrounding the tumor.

REFERENCES

1. Shapiro HM, Whyte SR, Harris AB, Galindo A. Acute intraoperative intracranial hypertension in neurosurgical patients: mechanical and pharmacological factors. Anesthesiology 1972;37:399–405.
2. Haar FL, Sadhu VK, Pinto RS, Gildenberg PL, Sampson JM. Can CT scan findings predict intracranial pressure in closed head injury patients? In: Shulman K, Marmarou A, Miller JD, et al, eds. Intracranial pressure IV. New York: Springer-Verlag, 1980:48–53.

Effect of Swan-Ganz Catheter Location on Accuracy of Wedge Pressure during PEEP

Swan-Ganz catheters (No. 7, Edwards Laboratories) were placed in 30 patients just before open heart surgery. The catheters were inserted transcutaneously into the internal jugular vein and advanced, using the flow-directed balloon. In all 30 patients, a metal clip was placed on the left atrium at its junction with the right upper lobe pulmonary vein during surgery. Postoperatively, the relative positions of the catheter tip and the left atrial marker were determined using a portable supine lateral chest roentgenogram taken immediately before hemodynamic measurements. Left atrial catheters were inserted in 12 patients. In 13 patients (43%) the Swan-Ganz catheter tips lodged within 1 cm of or above the left atrium. When in this position the wedge pressure measured by the catheter was not an accurate estimate of left atrial pressure when positive end-expiratory pressure (PEEP) was used, especially when left atrial pressure was low. Catheters located below the left atrium were accurate at all levels of PEEP tested. The position of Swan-Ganz catheters should be confirmed by a lateral chest roentgenogram when PEEP is used, and catheter tips not below the left atrium should be repositioned. (*Shasby DM, Dauber IM, Pfister S, et al. Swan-Ganz catheter location and left atrial pressure determine the accuracy of the wedge pressure when positive end-expiratory pressure is used. Chest 1981;80:666–70*)

ANESTH ANALG
1982;61:434-8

Antidiuretic and Growth Hormone Responses during Coronary Artery Surgery with Sufentanil-Oxygen and Alfentanil-Oxygen Anesthesia in Man

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DE LANGE, S., BOSCOE, M. J., STANLEY, T. H., DE BRUIJN, N., PHILBIN, D. M., AND COGGINS, C. H.: Antidiuretic and growth hormone responses during coronary artery surgery with sufentanil-oxygen and alfentanil-oxygen anesthesia in man. Anesth Analg 1982;61:434-8.

Antidiuretic hormone (ADH), growth hormone (GH), and cardiovascular responses to large (anesthetic) doses of alfentanil (1.2 ± 0.02 mg/kg) and oxygen and sufentanil (13.1 ± 0.4 μg/kg) and oxygen were measured before and during surgery (including cardiopulmonary bypass) and at the end of surgery in 29 patients undergoing coronary artery bypass surgery. The data demonstrate that alfentanil-O_2 and sufentanil-O_2 result in little change in cardiovascular dynamics throughout anesthesia and surgery, and also prevent changes in plasma levels of ADH and GH at all times during the study. Our findings contrast with previous studies with other anesthetics, including fentanyl, in which plasma levels of ADH and GH become markedly elevated during bypass. The results suggest that alfentanil and sufentanil may block hormonal stress responses to surgical stimulus better than fentanyl does. The clinical significance of the difference in ADH and GH responses during fentanyl and during alfentanil or sulfentanil anesthesia remains to be determined. However, this difference may provide part of the explanation why alfentanil and sufentanil-O_2 anesthesia require less frequent employment of other anesthetic adjuvants and are easier to use than fentanyl during coronary artery surgery.

Key Words: ANESTHESIA: cardiovascular; SURGERY: coronary artery bypass; ANESTHETICS, Intravenous: sufentanil, alfentanil, fentanyl; HORMONES: antidiuretic hormone, growth hormone.

ALFENTANIL and sufentanil, potent synthetic narcotics related to fentanyl, have recently been suggested as alternatives to fentanyl in patients undergoing open heart surgery with a narcotic-oxygen technique (1-3). The major advantages of alfentanil are its rapid onset of action, allowing a fast curtailment of an evoked cardiovascular stress response, and its short duration of action (fast recovery) (1, 4, 5). The advantage of sufentanil is that it has a higher potency than fentanyl, which results in a greater blockade of cardiovascular stress responses during surgery and enhances cardiovascular stability (2, 4, 5).

Antidiuretic hormone (ADH) and growth hormone (GH) are two of the body's stress-responding hormones. Plasma concentrations of these hormones usually increase during anesthesia and surgery (6, 7). It has been demonstrated that fentanyl-O_2 anesthesia blocks increases in plasma levels of ADH and GH which occur during cardiac surgery before cardiopulmonary bypass but not those that occur during bypass (8, 9). ADH and GH responses to alfentanil-O_2 and sufentanil-O_2 anesthesia before and during surgery and during and after cardiopulmonary bypass have

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This work was supported in part by Stanley Research Foundation.

Received from the Department of Anesthesiology, The University Hospital of Leiden, The Netherlands; Department of Anesthesiology, The University of Utah School of Medicine, Salt Lake City, Utah; and Departments of Anesthesiology and Medicine, Massachusetts General Hospital, Boston, Massachusetts. Accepted for publication January 19, 1982.

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not been reported and were investigated in this study in 29 patients undergoing coronary artery bypass surgery.

Methods

Institutional approval was obtained from the University Hospital of Leiden Ethics Committee, and all patients provided informed consent at the preoperative visit. Sixteen patients were randomly scheduled to receive alfentanil-O_2 (group I) and 13 sufentanil-O_2 (group II) as the sole anesthetic agents. Patients included in the study were A.S.A. physical status class III scheduled to undergo two or more vessel coronary artery revascularization. The patients were unselected with respect to preoperative cardiovascular dynamics, but all happened to have resting cardiac output greater than 4 L/min. None had evidence of significant hepatic, renal, pulmonary, or central nervous system pathology. Twelve of group I and 10 of group II patients were taking propranolol orally (80 to 120 mg, daily in divided doses) or equivalent doses of some other beta-adrenergic blocking compound; 11 of group I and 10 of group II patients were also taking some oral vasodilator before surgery.

All patients were premedicated with oral lorazepam (0.08 mg/kg) 2 hours before and intramuscular atropine (0.1 mg/15 kg) 30 minutes before arrival in the operating room. Patients taking a beta-blocking drug received their usual dose of the compound at the time of the oral premedication. Upon arrival in the operating room, catheters were placed in a hand vein and a radial artery and a bipolar lead II electrocardiogram was continuously recorded. Before induction of anesthesia, a flow-directed balloon-tipped thermodilution pulmonary arterial catheter (Instrumentation Laboratories, triple-lumen 110-cm model 44166 7F) was introduced into the pulmonary artery through an antecubital vein in an upper extremity using a #7 French Cordis introducer.

After a 5-minute stabilization period and while breathing oxygen, control measurements of heart rates (beats/min), cardiac output (L/min) (measured via thermodilution with 10 ml of 10 to 15°C dextrose, 5%, in water as the injectate), systolic and mean arterial (torr), and mean pulmonary arterial (torr) pressures (pulmonary arterial wedge pressures were not recorded because in some patients it was impossible to wedge the catheter at all of the protocol-prescribed intervals throughout the study) were made. Two minutes later pancuronium (0.02 mg/kg) was administered intravenously. Three minutes after pancuronium administration, patients in group I were given alfentanil, 3.0 mg/min, and patients in group II were given sulfentanil, 300 μg/min, intravenously. Respirations were first spontaneous, then assisted, and finally controlled (using a face mask and semi-closed system) to maintain Pa_{CO_2} at 35 to 40 torr (as measured in radial arterial blood every 15 to 30 minutes or estimated via continuous end tidal P_{CO_2} analysis). During infusion of alfentanil and sufentanil patients were requested to open their eyes and/or take a deep breath every 5 to 10 seconds. Failure to respond to three consecutive requests was equated with unconsciousness. When unconscious, the patients were paralyzed with intravenous succinylcholine (1.5 mg/kg) and their tracheas intubated with a cuffed Portex endotracheal tube. After intubation an amount of alfentanil or sufentanil equal to the dose producing unconsciousness was infused over the next 30 minutes. Additional alfentanil (2.5-mg bolus doses) or sufentanil (in 50-μg bolus doses) was given intravenously throughout surgery whenever systolic arterial blood pressure increased 15% or more above control values.

Patients were paralyzed with pancuronium (0.08 mg/kg slowly intravenously) 15 minutes after they had received succinylcholine. Paralysis was maintained with 0.04-mg/kg increments of pancuronium every 45 to 60 minutes until cardiopulmonary bypass. A saline-glucose solution (4.5% glucose and 0.1% normal saline in water) was administered at a rate of 1000 ml/hr during preanesthetic preparations and 200 to 250 ml/hr throughout the remainder of the operation. Whole blood was given after cardiopulmonary bypass and in the postoperative period to maintain right atrial pressure and/or pulmonary arterial diastolic pressure at preanesthetic values. The extracorporeal system was primed with Ringer's solution (1500 ml) and glucose 5% in water (500 ml) and 500 ml of a solution containing 100 g of albumin and 5000 units of heparin. Patients were cooled to 26 to 28°C during extracorporeal support and rewarmed to 37°C at its conclusion.

The surgical procedure began 30 minutes after anesthetic induction and intubation. Venous blood samples (12 ml) were obtained for ADH and GH assays and cardiovascular dynamics were recorded before anesthetic induction, 5 minutes after tracheal intubation, immediately before incision, 5 minutes after incision, 5 and 10 minutes after maximal sternal spread, just before beginning cardiopulmonary bypass, after 30 and 60 minutes of bypass, and at the end of surgery.

Plasma levels of ADH were assayed by the radioim-

munoassay technique of Philbin and co-workers (9) and plasma levels of GH by the radioimmunoassay technique of Peake (11). Data were analyzed for statistical significance using analysis of variance for comparison with control values and Student's unpaired *t*-test for analyses between groups; $p < 0.05$ was considered statistically significant.

Results

The mean ages [53 ± 8 (SD) years] weights (71 ± 10 kg), preoperative cardiovascular dynamics, and preoperative plasma ADH and GH values of the two groups were similar (Table). Unconsciousness was produced by an average of 44 ± 7 μg/kg of alfentanil or 4.1 ± 0.8 μg/kg of sufentanil. Narcotic requirements for the entire operation averaged 1.2 ± 0.02 mg/kg of alfentanil or 13.1 ± 0.4 μg/kg of sufentanil.

Cardiovascular dynamics were little changed at most prescribed study intervals in both groups (Table). The only significant changes occurred in the group receiving alfentanil 10 minutes after maximal sternal spread, when systolic arterial blood pressure increased significantly, and in both groups during bypass, when mean arterial blood pressure decreased significantly when compared with control values. The clinical impression was that sufentanil was easier to use than alfentanil because bolus doses were required much more frequently with alfentanil than with sufentanil. Also, sudden increases of arterial blood pressure with maximum surgical stimulation occurred more often during alfentanil anesthesia. Although these increases rapidly responded to additional alfentanil so that mean readings obtained at most prescribed study intervals were not different from control values, the anesthetic course was smoother with sufentanil because there were rarely rapid increases in arterial pressure at similar stressful periods.

Plasma levels of ADH and GH were not significantly changed from preanesthetic (control) values by alfentanil or sufentanil during anesthetic induction, intubation, at any time during the operation (including the period of cardiopulmonary bypass, or at the end of operation (Table).

TABLE

Cardiovascular and Antidiuretic Hormone Responses during Alfentanil-O_2 and Sufentanil-O_2 Anesthesia and Surgery*

	Control	After intubation	Before incision	After incision	After sternal spread	Before bypass	Bypass		End of operation
							30 min	60 min	
Heart rate (beats/min)									
Alfentanil	68	64	61	63	69	71			76
	±7	±7	±8	±8	±9	±8			±6
Sufentanil	66	61	63	66	67	64			69
	±6	±5	±6	±5	±8	±8			
Cardiac output (L/min)									
Alfentanil	5.7	5.4	6.0	5.9	6.0	5.6			6.2
	±0.7	±0.7	±0.8	±0.7	±.0.8	±0.9			±0.9
Sufentanil	5.5	5.3	5.3	5.5	5.7	5.8			5.9
	±0.8	±0.6	±0.6	±0.8	±0.7	±0.8			±0.8
Systolic arterial pressure (torr)									
Alfentanil	129	122	129	130	143†	136			135
	±11	±9	±8	±9	±12	±8			±10
Sufentanil	125	120	123	127	131	127			129
	±10	±9	±8	±10	±9	±10			±9
Mean arterial pressure (torr)									
Alfentanil	90	86	87	90	96	94	72†	77†	93
	±9	±8	±9	±9	±9	±8	±22	±18	±7
Sufentanil	86	82	84	87	89	87	70†	75†	84
	±8	±7	±8	±9	±4	±6	±6	±6	±7
Mean pulmonary artery pressure (torr)									
Alfentanil	17	19	19	18	20	18			19
	±3	±2	±2	±2	±2	±2			±2
Sufentanil	16	16	15	16	15	14			15
	±2	±2	±2	±2	±2	±1			±2
ADH (pg/ml)									
Alfentanil	11.9	8.0	7.7	7.8	8.5	8.3	8.4	8.1	11.4
	±2.4	±1.9	±1.7	±1.9	±2.0	±2.2	±1.8	±1.7	±2.1
Sufentanil	8.1	6.7	7.4	7.5	9.2	8.6	7.9	7.0	8.7
	±2.9	±1.8	±1.5	±1.8	±2.1	±2.0	±1.9	±2.0	±2.0
GH (ng/ml)									
Alfentanil	4.4	4.0	3.6	3.8	4.0	4.8	5.6	5.8	5.4
	±1.4	±1.0	±0.8	±0.8	±1.1	±1.4	±1.4	±1.4	±1.8
Sufentanil	4.0	3.6	3.8	4.0	4.2	4.4	4.6	4.2	4.6
	±1.0	±1.2	±1.0	±1.2	±1.0	±0.8	±1.2	±1.0	±1.0

* Values are means ± SD. Abbreviations used are: ADH, antidiuretic hormone; GH, growth hormone.
† $p < 0.05$, analysis of variance when compared with control values.

No patient remembered any aspect of laryngoscopy, intubation, or the operation. All patients were conscious within 6 hours of the end of surgery.

Discussion

The results of this study demonstrate that like high dose fentanyl (70 to 100 μg/kg) oxygen anesthesia (8), alfentanil-oxygen and sufentanil-oxygen anesthesia produces few changes in cardiovascular dynamics during coronary artery surgery. In addition, these new narcotics block increases in levels of ADH and GH with induction of anesthesia, intubation, and surgical stimulation until cardiopulmonary bypass, as has been found with fentanyl. Unlike fentanyl, however, alfentanil and sufentanil also block increases in levels of ADH and GH during cardiopulmonary bypass and the postbypass period. Our data suggest, therefore, that anesthetic doses of alfentanil and sufentanil may be more effective than fentanyl in blocking hormonal "stress responses" during surgery.

More than 6-fold increases in ADH and GH occur during cardiopulmonary bypass in patients undergoing coronary artery bypass operations with fentanyl-O_2 anesthesia (8, 9). Similar or greater increases in levels of ADH have been found during bypass in similar patients anesthetized with halothane or with small doses of fentanyl (0.5 to 1.2 μg/kg) plus halothane or other narcotics (9, 10) (Wu W, Zbuzkova V. Vasopressor levels during cardiac surgery. Annual Meeting of the American Society of Anesthesiologist, October 17–19, 1977, New Orleans, Louisiana, p 585). The mechanism(s) producing increases in levels of ADH and GH during bypass is unknown. It has been suggested that introduction of the unknown physiologic state of cardiopulmonary bypass produces a marked stress response which results in an increased output of ADH (12). Plasma levels of catecholamines, cortisol, and other stress-responding hormones are also markedly increased during bypass (9, 13–16). Interestingly, addition of pulsatile flow during extracorporeal circulation attenuates but does not eliminate increases in ADH levels during bypass (17). Similarly, addition of blood to the normal crystalloid (lactated Ringer's) priming volume of the extracorporeal circuit, changing the contents of the crystalloid prime, and rewarming during extracorporeal circulation do not prevent these changes.

Why alfentanil and sufentanil block increases in ADH and GH level during bypass while fentanyl does not is unclear from our data. A possible explanation could be that the relative doses of the newer narcotics in this study were greater than were used in our past study with fentanyl. Alfentanil is reported to be one third to one fourth as potent and sufentanil, 5 to 10 times as potent as fentanyl (2, 4, 5). In our previous investigation (8) an average of 71 μg/kg of fentanyl was used for the entire operation. Similarly, Walsh and colleagues (9) used 75 μg/kg of fentanyl in their study. In this investigation, 1200 μg/kg of alfentanil and 13 μg/kg of sufentanil were used. These dosages are proportionately more than 4 times (alfentanil) and almost twice (sufentanil) as much as the dosages used with fentanyl in previous studies when correction is made for potency differences in the drugs. Philbin and Coggins (12) have demonstrated that increases in depth of anesthesia that occur after higher doses of morphine are more effective than lower doses of morphine in inhibiting ADH responses to surgical stimulation. If this is also true with fentanyl-like drugs, then the blockade of increases in plasma levels of ADH and GH during bypass as occurred with alfentanil and sufentanil in this study should also occur with higher doses of fentanyl. However, recent, as yet unpublished data (Salt Lake City, Utah), using doses of 150 to 200 μg/kg of fentanyl (2 to 3 times the dosage of fentanyl used in our last study), and data from Bovill and Sebel (Amsterdam, The Netherlands), using fentanyl doses in the range of 100 to 120 μg/kg document that even in enormous doses, fentanyl does not prevent increases in levels of ADH and GH during cardiopulmonary bypass.

Whether inhibition of increases in levels of ADH and GH during cardiopulmonary bypass and in the postoperative period is beneficial for patients is not known. At high plasma concentrations ADH is a potent vasoconstrictor and an antidiuretic (18–20). Peripheral vasoconstriction and antidiuresis were not evident during and after bypass in this study nor have they been observed during these periods with high dose fentanyl-O_2 anesthesia (8, 13). Therefore, the clinical implications of blocking decreases in plasma levels of ADH during cardiopulmonary bypass are unknown at this time.

Plasma levels of epinephrine, norepinephrine, dopamine, cortisol, and other "stress-evoked" hormones were not measured in this study because of the large blood sampling volumes that would have been required for plasma analysis of all these hormones. However, absence of changes in plasma levels of ADH and GH during anesthesia and surgery is usually associated with no change or a decrease in plasma concentrations of the catecholamines and cortisol and increases in plasma levels of ADH and GH with

increases in plasma concentrations of the catecholamines and cortisol irrespective of the anesthetic technique (8, 9, 12, 13, 21). Fentanyl has been shown to prevent increases in levels of plasma catecholamines and cortisol until, but not during, bypass (9, 13). There are no reports as to how alfentanil and sufentanil affect these hormones during bypass. Preliminary findings from Sebel and Bovill (personal communication), as well as recent data obtained from our own patients (de Lange S, Stanley TH, unpublished data), suggest that alfentanil and sufentanil may not block increases in plasma levels of catecholamines during cardiopulmonary bypass. If final reports confirm these early findings then alfentanil and sufentanil may prove not to be significantly greater blockers of surgical-induced "hormonal stress responses" than fentanyl. However, if final reports demonstrate that alfentanil and sufentanil either block or lessen hormonal stress responses during and after cardiopulmonary bypass, requirements for vasodilators, antihypertensive medications, and/or beta blockers during these periods and after surgery may be reduced and recovery faster or less complicated. There are data that indicate that, at least with sufentanil, requirements for vasodilators and antihypertensives during and after bypass are significantly decreased and intraoperative management is less difficult when compared with equivalent doses of fentanyl (2).

In conclusion, our data in this study demonstrate that high doses of alfentanil and sufentanil produce stable cardiovascular dynamics and block increases in levels of ADH and GH during anesthesia, throughout surgery (including cardiopulmonary bypass), and at the end of surgery. This contrasts previous findings with all other anesthetics including fentanyl and suggests that alfentanil and sufentanil may be more effective than other anesthetics in blocking hormonal stress responses to surgical stimulus. The clinical significance of the difference in ADH and GH responses during fentanyl and during alfentanil or sufentanil anesthesia remains to be determined but may mean that alfentanil and sufentanil-O_2 anesthesia require less frequent employment of other anesthetic adjuvants and are thus easier to use than fentanyl.

REFERENCES

1. de Lange S, Stanley TH, Boscoe MJ. Alfentanil-oxygen anaesthesia for coronary artery surgery. Br J Anaesth 1981;53: 1291–6.
2. deLange S, Stanley TH, Boscoe MJ. Comparison of sufentanil-O_2 and fentanyl-O_2 for coronary artery surgery. Anesthesiology 1982;56:112–8.
3. Sebel PS, Bovill JG, Wauquier A. Total narcotic anesthesia with sufentanil. Anesth Analg 1981;60:276.
4. de Castro J, Van de Water A, Wouters L, Xhonneux R, Reneman R, Kay B. Comparative study of cardiovascular, neurological and metabolic side effects of eight narcotics in dogs. Acta Anaesthesiol Belg 1979;30:5–99.
5. de Castro J. Practical application and limitation of analgesic anaesthesia. Acta Anaesthesiol Belg 1976;27:107–28.
6. Hall GM, Young C, Holdcroft A, Alaghband-Zadek K. Substrate mobilization during surgery: a comparison between halothane and fentanyl anaesthesia. Anaesthesia 1978;33:924–30.
7. Hall GM. Fentanyl and the metabolic response to surgery. Br J Anaesth 1980;52:561–2.
8. Stanley TH, Philbin DM, Coggins CH. Fentanyl-oxygen anaesthesia for coronary artery surgery: cardiovascular and antidiuretic hormone responses. Can Anaesth Soc J 1979;26:168–71.
9. Walsh ES, Paterson JL, Riordan O, Hall GM. Effect of high-dose fentanyl anaesthesia on the metabolic and endocrine response to cardiac surgery. Br J Anaesth 1981;53:1155–65.
10. Philbin DM, Wilson NE, Sokolski J, Coggins C. Radioimmunoassay of antidiuretic hormone during morphine anaesthesia. Can Anaesth Soc J 1976;23:290–5.
11. Peake GT. Growth hormone. In: Jaffe BM, Behrman HR, eds. Methods of hormone radioimmunoassay. New York: Academic Press, 1974:103–23.
12. Philbin DM, Coggins CH. Plasma antidiuretic hormone levels in cardiac surgical patients during morphine and halothane anesthesia. Anesthesiology 1978;49:95–8.
13. Stanley TH, Berman L, Green O, Robertson D. Plasma catecholamine and cortisol responses to fentanyl-oxygen anesthesia for coronary artery operations. Anesthesiology 1980;53:250–3.
14. Anton AH, Gravenstein JS, Wheat MW. Extracorporeal circulation and endogenous epinephrine and norepinephrine in plasma, atrium and urine in man. Anesthesiology 1964;25: 262–9.
15. Replogle R, Levy M, De Wall RA, Lillihie C. Catecholamine and serotonin response to cardiopulmonary bypass. J Thorac Cardiovasc Surg 1962;44:638–48.
16. Sebel PS, Bovill JG, Schellekens APM, Hawker CD. Hormonal responses to high dose fentanyl anaesthesia: a study in patients undergoing cardiac surgery. Br J Anaesth 1981;53:941–8.
17. Philbin DM, Levine FH, Kono K, et al. Attenuation of stress response of cardiopulmonary bypass by the addition of pulsatile flow. Circulation (in press 1982).
18. Moran WH Jr. CPPB and vasopressor secretion (editorial). Anesthesiology 1971;34:501–4.
19. Corliss RJ, McKenna DH, Sailer S, O'Brien GS, Rowe GG. Systemic and coronary hemodynamic effects of vasopressin. Am J Med Sci 1968;256:293–9.
20. Edmunds R, West JB. A study on the effect of vasopressin on portal and systemic blood pressure. Surg Gynecol Obstet 1962;114:458–62.
21. Kono K, Philbin DM, Coggins CH, et al. Renal function and stress response during halothane or fentanyl anesthesia. Anesth Analg 1981;60:552–7.

ANESTH ANALG
1982;61:439-41

Use of 100-Hertz Tetanus as an Index of Recovery from Pancuronium-Induced Non-depolarizing Neuromuscular Blockade

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KOPMAN, A. F., EPSTEIN, R. H., AND FLASHBURG, M. H.: Use of 100-hertz tetanus as an index of recovery from pancuronium-induced non-depolarizing neuromuscular blockade. Anesth Analg 1982;61:439-41.

During recovery from non-depolarizing neuromuscular blockade the evoked response to train-of-four (TOF), 100-Hz tetanus (T_{100}) and 50-Hz tetanus (T_{50}) was measured in 10 patients. When the TOF fade ratio exceeded 0.70, tetanic tension to T_{50} was well sustained. However, even at TOF ratios as high as 0.88 a 2-second tetanic response to T_{100} showed marked fade. T_{100} stimulation appears to be too sensitive a test of residual curarization for routine clinical use. Fade on T_{100} may be quite apparent at a time when the use of additional neuromuscular antagonists are not indicated and may be counterproductive.

Key Words: ANTAGONISTS, Neuromuscular relaxants: edrophonium; MEASUREMENT TECHNIQUES: neuromuscular blockade; MONITORING: stimulator, nerve; NEUROMUSCULAR RELAXANTS: pancuronium.

SINCE the introduction of competitive neuromuscular blockers into anesthetic practice, there has been a continuing debate over how the clinician can most reliably judge the adequacy of recovery from these drugs at the end of surgery. The evoked response to 100-Hz tetanic stimulation (T_{100}) has been one of the most controversial indices of recovery suggested for clinical use.

There is widespread acceptance among practicing anesthesiologists that this test is the most sensitive available and is a useful tool in day-to-day practice. The manufacturer of the largest line of portable nerve stimulators commercially available recently told the senior author that he has introduced two models incorporating 100-Hz tetanus because of consumer demand. The work of Gissen and Katz (1), Waud and Waud (2, 3), and Zeh and Katz (4) supports the contention that the evoked response to 100-Hz stimulation is a sensitive index of residual curarization. Ali et al (5), however, take the position that frequencies greater than 70 Hz are nonphysiologic and have no clinical validity.

There is a considerable body of evidence to show that if the train-of-four (TOF) fade ratio has returned to a value of 0.70 or greater that muscle strength and respiratory mechanics are essentially normal and that, for all practical purposes, clinical recovery is complete. Ali et al (5) have recently demonstrated that, when TOF is equal to or greater than 0.70, 50-Hz tetanus (T_{50}) is well maintained. We have not, however, been able to find any published reports measuring the degree of tetanic fade to 100-Hz stimulation when TOF stimulation suggests that recovery is adequate. It has been our clinical impression that T_{100} frequently shows obvious fade at this time. We, therefore, decided to compare TOF fade with tetanic tension at 100 Hz for 2 seconds at times when the TOF ratio exceeded 0.70 following recovery from pancuronium-induced paralysis.

Methods

Ten patients undergoing elective surgical procedures in whom the administration of a muscle relaxant was indicated by the nature of the surgical procedure,

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Received from the Department of Anesthesiology, Long Island Jewish Hillside Medical Center, New Hyde Park, New York. Accepted for publication January 21, 1982.

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were studied. Premedication consisted of atropine, 0.4 mg; meperidine, 25 to 50 mg; and secobarbital, 50 to 100 mg. Anesthesia was induced with thiamylal sodium and maintained with nitrous oxide and oxygen plus halothane (average maintenance concentration 0.5% to 1.0% inspired). Tracheal intubation was performed with succinylcholine, 0.75 to 1.0 mg/kg. Ventilation was controlled at a tidal volume of 10 ml/kg at a rate of 10 breaths per minute. Body temperature ranged from 35.5 to 36.5°C. Evoked isometric twitch tension to ulnar nerve stimulation was measured with a Grass FT-10 linear force transducer and a Gould polygraph. Supramaximal stimuli of 0.2 msec were delivered via needle electrodes at the wrist in trains-of-four (four stimuli at intervals of 0.5 sec) from a Grass S 48 stimulator via a SIU-5 isolation unit. When single twitch height had recovered from the intubating dose of succinylcholine and remained stable for at least 5 minutes, control measurements of TOF fade ratio and tetanic response to 50- and 100-Hz stimulation (2-second duration) were made. Control TOF fade ratio always exceeded 0.95 and control tetanic contractions at both frequencies were fully sustained. The initial dose of pancuronium given was 0.04 mg/kg. Additional increments of relaxant were given as needed to maintain good clinical relaxation and operating conditions. An attempt was made, however, to time incremental doses so that the train-of-four fade ratio was in excess of 0.10 at the termination of the procedure. Reversal of neuromuscular blockade was accomplished with 5-mg increments of edrophonium until the TOF fade ratio exceeded 0.70. No tetanic stimuli were delivered until this was accomplished. When the TOF ratio was equal to 0.70 or more a supramaximal tetanus of 100 Hz for 2 seconds was delivered and response recorded. TOF fade ratios were then remeasured at 10-second intervals until stable. A 50-Hz tetanus of 2 seconds duration was then administered. After TOF fade ratios had again stabilized a final 100-Hz tetanus was given and response recorded. The minimum interval between tetanic trains was 90 seconds. Train-of-four fade ratio was calculated as the height of the fourth twitch divided by the height of the first twitch in the train. The tetanic fade ratio was expressed as the amplitude of the response at the end of 2 seconds divided by the peak height obtained.

Results

The TOF fade ratio was easily reversible to 0.70 or greater in all patients with 0.20 to 0.35 mg/kg of edrophonium. Tetanic response to T_{50}, was, as expected, well sustained. During a 2-second train, peak developed tension declined an average of only 7%.

Tetanic fade with 100-Hz stimulation, on the other hand, was quite marked in all our subjects (Table). At a time when the TOF fade ratio was in excess of 0.70, peak tetanic tension declined an average of 72%. Three patients showed decreases in tetanic tension of 84% or more [Figure (patient 9)]. This degree of fade is obvious by either visual inspection of the hand or palpation of the abducted thumb. The small amounts of fade measured with T_{50} stimulation cannot be subjectively appreciated unless the response is recorded via a force transducer (unpublished data, 1981).

There was no significant difference in the amount of fade recorded between the first and second T_{100}

TABLE

Tetanic Fade to 100-Hz and 50-Hz Stimulation as Function of Train-of-Four (TOF) Response

Patient no.	TOF fade ratio	Tetanic fade*	
		100 Hz	50 Hz
1	0.79	0.16	0.94
2	0.74	0.36	0.91
3	0.82	0.28	0.95
4	0.73	0.37	0.93
5	0.70	0.34	0.96
6	0.81	0.32	0.89
7	0.85	0.15	0.89
8	0.88	0.35	1.00
9	0.82	0.09	0.85
10	0.75	0.39	0.95
Mean ± SEM	0.79 ± 0.02	0.28 ± 0.04	0.93 ± 0.02

* Tetanic tension after 2 sec/peak tetanic tension.

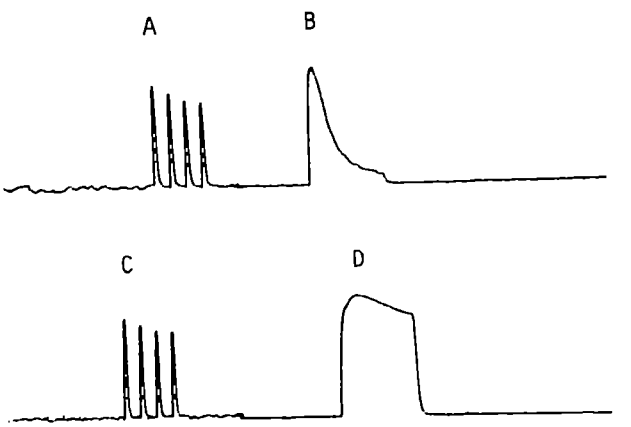


FIGURE. Decrease in tetanic tension (patient 9). When train-of-four (TOF) fade ratio had returned to 0.82 (A), a 100-Hz tetanus (T_{100}) of 2 seconds duration had a fade ratio of 0.09 (B). Two minutes later TOF again is 0.82 (C). A 50-Hz tetanus (T_{50}) at this time shows fade ratio of 0.85 (D). Elapsed time between TOF stimulation and following tetanic trains is >10 seconds (paper speed slowed during this interval). Polygraph sensitivity reduced 5 times during recordings of tetanic response.

trains. The T_{50} tetanus, therefore, did not have any measurable conditioning effect on a subsequent tetanic train delivered 90 seconds later.

Discussion

The demonstration by Gissen and Katz (1) in 1969 that the evaluation of neuromuscular block by tetanic response was more sensitive that twitch alone was a valid one. Their conclusion that the evoked responses to 100- and 200-Hz tetanic stimuli are more sensitive than the 50-Hz response to small degrees of residual blockade remains unchallenged. However, no information of a quantitative nature can be drawn from their classic paper because much of their methodology would no longer be acceptable. Single-twitch stimulation rates were set at 0.3 Hz and tetanic trains were delivered at 10-second intervals. It is probable that both single-twitch and tetanic responses were subject to conditioning by previous stimuli. The 1.5-msec pulse duration that they used is also excessive by today's standards. A greater problem was their use of the FT-03 force transducer. This unit would almost certainly have been overloaded by a supramaximal tetanus given for only 0.5 second. As a result, tetanic fade at 50 Hz if present might very well have been missed. Finally, train-of-four stimulation had not yet been described and so was not studied by these investigators. No evidence was presented, by the authors, to substantiate the suggestion that rates of stimulation of 100 Hz and higher were more useful in uncovering clinically significant amounts of muscular weakness than the 50-Hz tetanus.

Stanec et al (6) recently have shown that during balanced anesthesia, in the absence of any relaxants, evoked peak tetanic tensions cannot be maintained if the frequency of stimulation is 60 Hz or higher. At 100 Hz, tetanic tension is reduced 20% at 5 seconds and 35% at 10 seconds. Their findings indicate that tetanic trains of 100 Hz and greater can be misleading as tetanic fade develops even in the absence of blocking drugs, if the train duration exceeds 1 to 2 seconds.

Clearly, as noted above, the evoked response to T_{100} tetanus is an extremely sensitive indicator of residual neuromuscular blockade. At TOF fade ratios as high as 0.88 we found easily detectable tetanic fade still present when a 100-Hz challenge was given. The important question, however, is whether this index of neuromuscular function is of any value to the clinician. The anesthetist who elicits a TOF fade ratio of greater than 0.7 and a strong, well sustained response to T_{50}, yet is faced with appreciable fade on 100-Hz stimulation has a problem, especially if the patient is not awake enough to cooperate with such tests as the voluntary head lift. Is fade on T_{100} an indication for the administration of additional reversal agents? We maintain that it is not, if it stands alone as the only indication of residual paresis. There is no evidence to indicate that return to a TOF ratio of 0.70 or greater following reversal is not equivalent to full recovery of normal respiratory reserve. At this value vital capacity, inspiratory force, and peak expiratory flow rates are all at or approaching control values (7), and sustained eye opening, hand grasp, and head lift are also present (8). As T_{100} may indicate paresis at a time when in reality the patient has full return of muscular strength, we believe that the test can be misleading. At best it may cause undue worry; at worst, it can induce the anesthetist to administer additional drugs that are not indicated and may actually be counterproductive. Payne, Hughes, and Al Azawi (9) recently demonstrated that a repeat dose of 2.5 mg of neostigmine, administered to patients whose paresis has been reversed from a non-depolarizing neuromuscular blockade, will diminish peak tetanic tension and may produce marked fade to T_{50} stimulation. We, therefore, agree with Ali et al (5) that T_{100} as an "index of recovery" should be abandoned.

REFERENCES

1. Gissen AJ, Katz RL. Twitch, tetanus and post tetanic potentiation as indices of nerve-muscle block in man. Anesthesiology 1969;30:481–7.
2. Waud BE, Waud DR. The relation between tetanic fade and receptor occlusion in the presence of complete neuromuscular block. Anesthesiology 1971;35:456–64.
3. Waud BE, Waud BR. The relationship between the response to "train-of-four" stimulation and receptor occlusion in the presence of complete neuromuscular blockade. Anesthesiology 1972;37:413–6.
4. Zeh DW, Katz RL. A new nerve stimulator for monitoring neuromuscular blockade and performing nerve blocks. Anesth Analg 1978;57:13–7.
5. Ali HH, Savarese JJ, Lebowitz PW, Ramsey FM. Twitch, tetanus, and train-of-four as indices of recovery from non-depolarizing neuromuscular blockade. Anesthesiology 1981;54:294–7.
6. Stanec A, Heyduk J, Stanec G, Orkin LR. Tetanic fade and post-tetanic tension in the absence of neuromuscular blocking agents in anesthetized man. Anesth Analg 1978;57:102–7.
7. Ali HH, Wilson RS, Savarese JJ, Kitz RJ. The effect of tubocurarine on indirectly elicited train-of-four muscle response and respiratory measurements on humans. Br J Anaesth 1975; 47:570–4.
8. Brand JB, Ali HH, Cullen JB, Wilson NE. Spontaneous recovery from nondepolarizing neuromuscular blockade: correlation between clinical and evoked responses. Anesth Analg 1977;56:55–8.
9. Payne JP, Hughes R, Al Azawi S. Neuromuscular blockade by neostigmine in anaesthetized man. Br J Anaesth 1980;52:69–76.

ANESTH ANALG
1982;61:442–4

Effect of Bretylium on Neuromuscular Transmission

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WELCH, G. W., AND WAUD, B. E.: Effect of bretylium on neuromuscular transmission. Anesth Analg 1982;61:442–4.

The effect of bretylium on the response of an isolated muscle (guinea pig lumbrical) to direct and indirect stimulation was examined. An initial increase in twitch response to both indirect and direct stimulation was followed at higher concentrations of bretylium by block of the indirect response only. The ED_{50} for this latter effect was 106.9 ± 9.25 μM. However, in the presence of subthreshold levels of *d*-tubocurarine the Ed_{50} was markedly reduced to 1.31 ± 1.11 μM, a concentration that could occur during clinical use of bretylium. Thus, the physician is cautioned to consider the possibility that neuromuscular block may be produced when bretylium is administered in close temporal proximity to neuromuscular blocking agents.

Key Words: NEUROMUSCULAR RELAXANTS: bretylium, *d*-tubocurarine.

BRETYLIUM is a bromobenzyl quaternary ammonium compound which was originally used in the late 1950s for the treatment of hypertension. Because of inconsistent oral absorption and relative ineffectiveness, it is no longer used for this purpose. However, in the mid-1960s, significant cardiac antiarrhythmic properties were demonstrated and intravenous bretylium has recently been introduced in this country for the treatment of refractory ventricular dysrhythmias (1).

Examination of the molecular structure of bretylium proves interesting (Fig 1). The drug is remarkably similar to edrophonium and might therefore be expected to demonstrate some anticurare effects. Bretylium too may be considered an analogue of choline and has been shown to inhibit acetylcholine synthesis (2). Also the presence of a quaternary ammonium structure is generally associated with an effect on neuromuscular transmission (3), whereas benzoquinonium, a drug with two ends resembling bretylium, has been shown to have both competitive and depolarizing activity (4). Bretylium, in rat phrenic nerve-diaphragm preparations, has been shown to produce an increased twitch response with stimulation at a rate of one shock per 10 seconds and block with stimulation at a rate of once per second (5). In a small percentage of patients, muscle weakness has been reported during prolonged therapy (2).

Because bretylium may be used both during surgery and in the recovery room, and therefore in the presence of neuromuscular blocking agents, we decided to study the interaction of bretylium and *d*-tubocurarine.

Methods

Isolated guinea pig nerve-lumbrical muscle preparations (6, 7) were prepared by dissecting the intact nerve and lumbrical muscle from guinea pigs weighing between 300 and 400 g each. These preparations were placed in Krebs solution maintained at 37°C and bubbled with oxygen 95% and carbon dioxide 5%. Two sets of stimulating electrodes were added to the bath to allow for alternate direct and indirect stimulation. The resting muscle length was adjusted to give maximal developed tension. Stimuli were delivered once every 10 seconds with impulses of twice maximal intensity. The bathing solution was initially changed every 30 minutes, but subsequently, new solution was infused continuously. The reason for this change was that the rate of onset of action of bretylium was very slow so it was necessary to refresh the bathing solution more frequently than just when drug concentration was being changed. A continuous infusion al-

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Supported by grant NS12255 from the National Institute of Neurological and Communicative Disorders and Stroke.

Received from the Departments of Anaesthesia and Surgery, University of Massachusetts Medical School, and Departments of Anesthesiology and Pharmacology, University of Massachusetts Medical Center, Worcester, Massachusetts 01605. Accepted for publication January 26, 1982.

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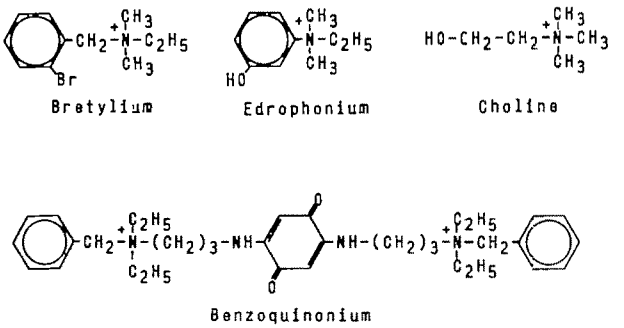


FIG 1. Structure of bretylium and related compounds.

lowed this to be done without producing periodic washing artifacts. After approximately 30 minutes for stabilization of the preparation, bretylium was added to the bath solution and the resulting steady-state effect on twitch response determined. Graded concentrations of bretylium were used with each preparation to generate a twitch height versus bretylium concentration-response curve, and the concentration of bretylium that blocked the twitch height by 50% (ED_{50}) was determined (7).

A second set of experiments was performed to generate bretylium concentration-response curves in the presence of *d*-tubocurarine 0.4 μM (a concentration that did not by itself affect twitch height).

Results

In low concentrations (50 to 100 μM) bretylium caused an increase in twitch response to both indirect (Fig 2) and direct stimulation. Initial stimulation was followed at higher concentrations by block of the response to indirect stimulation (Fig 2). There was no depression of the response of directly stimulated muscle. The time for initial onset of the paralysis was delayed and the time to reach steady state was much longer than that seen with *d*-tubocurarine. At equipotent concentrations, *d*-tubocurarine begins to block rapidly and steady state is reached within 1 hour. On the other hand, a blocking dose of bretylium begins to show its effect in 90 minutes and steady state is not reached for approximately 3 hours.

When a subthreshold concentration of *d*-tubocurarine was present, bretylium produced some neuromuscular block at a concentration of 1 μM and complete block by 10 μM (Fig 2).

The concentration of bretylium alone needed to block the twitch response by 50% (ED_{50}) is 106.9 ± 9.25 μM. In the presence of *d*-tubocurarine 0.4 μM (a concentration which, by itself, shows minimal effect on the twitch response), the ED_{50} of bretylium is 1.31 ± 1.11 μM—representing a marked potentiation of the

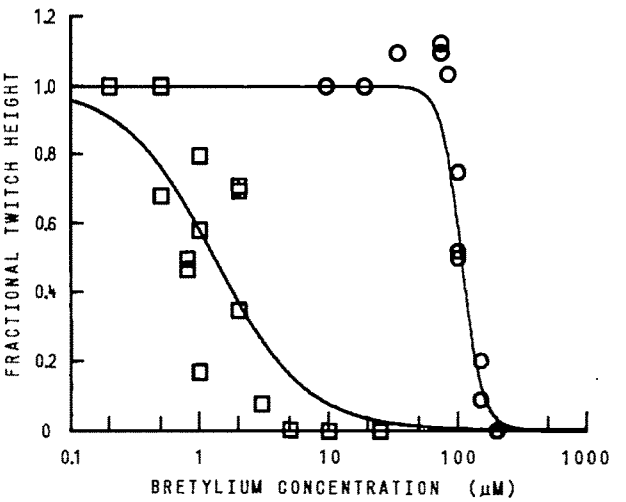


FIG 2. Concentration-response curves for bretylium. Guinea pig lumbrical muscle. Ordinates, twitch responses as fraction of control value; abscissae, concentrations of bretylium (μM); circles, responses to indirect stimulation (n = 15); squares, responses to indirect stimulation in the presence of 0.4 μM *d*-tubocurarine (a concentration with negligible effect by itself on twitch response) (n = 15). Curves are a least-squares fit (7) of logistic function $y = x^s/(x^s + k_s)$ a function producing a sigmoid curve of maximum = 1, ED_{50} = k, and slope governed by s.

effect of the bretylium. When, after 3 hours, bretylium was removed from the bath containing *d*-tubocurarine, there was further depression of the twitch height and no return of neuromuscular transmission until the *d*-tubocurarine was also removed from the bath. When bretylium and *d*-tubocurarine were simultaneously removed from the bath, the twitch response recovered rapidly. However, 20 minutes later, the addition of *d*-tubocurarine, 0.4 μM, caused a rapid depression, indicating that the effect of bretylium was still present.

Discussion

As observed by Green and Hughes (5), bretylium can, at fairly high concentrations, produce neuromuscular block. More significant is the marked potentiation produced by the presence of even a subthreshold concentration of *d*-tubocurarine. The plasma concentration of bretylium following a 300-mg intramuscular dose has been found to be 3 μM (8) and, following 10 mg/kg IV, 12 μM (American Critical Care, McGaw Park, IL, personal communication, 1979). Both these values are well above the concentration we found could begin to produce interference with neuromuscular transmission if the margin of safety had been compromised by the presence of a residual level of a drug like *d*-tubocurarine. This is particularly relevant in the clinical setting, for example the recovery room where a patient might not have evidence of frank

neuromuscular block yet still have an appreciable level of circulating neuromuscular blocking agent. If such a patient required antiarrhythmic therapy and bretylium were chosen, the setting would be analogous to that in our experiments and the possibility that the bretylium could seriously compromise neuromuscular transmission is great. Furthermore, the slow kinetics of action we observed could presumably occur in patients as well; this would aggravate the danger of this drug interaction. It might be several hours after administration of the bretylium before the neuromuscular block becomes manifest. Thus, the physician administering the bretylium must be aware that prolonged surveillance of the patient is indicated.

REFERENCES

1. Koch-Weser J. Drug therapy: bretylium. N Engl J Med 1979;300:473–7.
2. Bowman WC. Effects of adrenergic activators and inhibitors on skeletal muscles. In: Szekeres L, ed. Handbook of experimental pharmacology. Berlin: Springer-Verlag, 1980:47–128.
3. Waud BE, Waud DR. Physiology and pharmacology of neuromuscular blocking agents. In: Katz RL, ed. Muscle relaxants. New York: Elsevier, 1975:1–58.
4. Hoppe JO. A pharmacological investigation of 2,5-bis-(3-diethyl-amino propylamino) benzoquinone-bis-benzylchloride (Wen 2747): a new curariminetic drug. J Pharmacol Exp Ther 1950;100:333–45.
5. Green AF, Hughes R. Effects of adrenergic neurone blocking agents on voluntary muscle stimulated at different frequencies. Br J Pharmacol 1966;27:164–76.
6. Waud BE, Waud DR. Effects of volatile anesthetics on directly and indirectly stimulated skeletal muscle. Anesthesiology 1979;50:103–10.
7. Waud BE, Waud DR. Comparison of the effects of general anesthetics on the end-plate of skeletal muscle. Anesthesiology 1975;43:540–7.
8. Kuntzman R, Tsai I, Chang R, Conney AH. Disposition of bretylium in man and rat. Clin Pharmacol Ther 1970;11:829–37.

Epidural Morphine and Ventilatory Depression

Minute ventilation, end tidal P_{CO_2} (P_{ETCO_2}) and the ventilatory response to added CO_2 were measured before and at intervals up to 6 hours after epidural morphine, 3.5 mg and 7.0 mg, and before and after subcutaneous injections of the same dose in four volunteers. Subcutaneous morphine increased P_{ETCO_2} slightly, but did not alter the sensitivity of the response to added CO_2. Epidural morphine reduced ventilation and increased P_{ETCO_2} progressively with time and, 6 hours after injection, reduced the ventilatory response to CO_2 considerably. In two subjects tested, these ventilatory effects persisted for 24 hours. The added effects of epidural morphine were due primarily to reductions in tidal volume and the tidal volume response to added CO_2. The authors conclude that epidural morphine causes delayed and prolonged ventilatory depression, which is of a greater magnitude and a different ventilatory pattern than that which follows the same dose of morphine given subcutaneously. Ventilatory depression after lumbar epidural morphine develops slowly, as the lower limb analgesic effect is waning. (*Knill RL, Clement JL, Thompson WR. Epidural morphine causes delayed and prolonged ventilatory depression. Can Anaesth Soc J 1981;537–43*)

ANESTH ANALG
1982;61:445-8

Publications Resulting from Anesthesia Meeting Abstracts

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MERANZE, J., ELLISON, N., AND GREENHOW, D. E.: Publications resulting from anesthesia meeting abstracts. Anesth Analg 1982;61:445-8.

Of 55 abstracts presented at the 1979 annual meeting of the International Anesthesia Research Society (I.A.R.S.) 24 (43.6%) and of 62 abstracts presented at the 1980 annual meeting of the I.A.R.S. 25 (40.3%) were published by July 1, 1981. Of 324 abstracts presented at the 1978 annual meeting of the American Society of Anesthesiologists (A.S.A.) 98 papers (30.1%) were published by January 1, 1981. Eighty-two percent of the I.A.R.S. meeting papers and 66.7% of the A.S.A. papers were published in anesthesia journals, and the rest of the papers appeared in publications representing a variety of other disciplines. The average lag time between publication of the abstract and publication as an article was 8.2 months for I.A.R.S. abstracts and 12.2 months for A.S.A. abstracts. By July 1, 1981, four 1979 I.A.R.S. abstracts were filed in Science Citation Index (SCI) as cited reference and by January 1, 1981, fifty-six 1979 A.S.A. abstracts were filed.

Key Words: ABSTRACTS; PUBLICATIONS; CITATION ANALYSIS.

THE PRESENTATION of original research at the annual meetings of the International Anesthesia Research Society (I.A.R.S.) and the American Society of Anesthesiologists (A.S.A.) is one of the steps often taken between design and execution of a research protocol and publication of the completed work. Presumably publication of a manuscript in a peer-reviewed journal reaffirms the work's scientific validity, which had previously been suggested by the abstract's being selected for presentation at the meeting. With this in mind, we analyzed the publication patterns for all abstracts that were presented at the 1979 and 1980 annual meetings of the I.A.R.S. and at the 1978 annual meeting of the A.S.A. in order to determine the distribution of papers resulting from these abstracts. Abstracts for the 1978 A.S.A. annual meeting and the 1979 I.A.R.S. meeting were obtained from the abstract booklets distributed at the meeting.

Prior to 1979 abstracts were published in separate booklets distributed to registrants at the annual meetings or were available through society headquarters. Since 1979 abstracts have been published as a supplement to *Anesthesiology* and since 1980 they have been published as part of one of the monthly issues of *Anesthesia and Analgesia*. We also ascertained for these three meetings the number of times that annual meeting abstracts have been cited as references in subsequent papers as of July 1, 1981 for the I.A.R.S. meetings and as of January 1, 1981 for the A.S.A. meeting. We then characterized the abstract-citing journals as anesthesia and nonanesthesia.

Methods and Materials

We identified all abstracts presented in the three meetings. We then conducted a Medical Literature Analysis and Retrieval System (MEDLARS) search for all articles that were presented in peer-reviewed journals within 27 months after the 1979 I.A.R.S. and 1978 A.S.A. meetings and within 15 months after the 1980 I.A.R.S. meeting and which included among the authors the individual presenting the abstract. The 15 abstracts appearing in the 1978 Abstracts of Scientific Papers, but not presented at the A.S.A., were excluded. All papers identified by the search were then compared with the title of the abstract. If there was a possibility of the two being related they were compared for data and inclusive dates of study. SCI-search, the computerized database of Science Citation

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Received from the Robert Dunning Dripps Library of Anesthesia and Department of Anesthesia, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania. Accepted for publication January 19, 1982.
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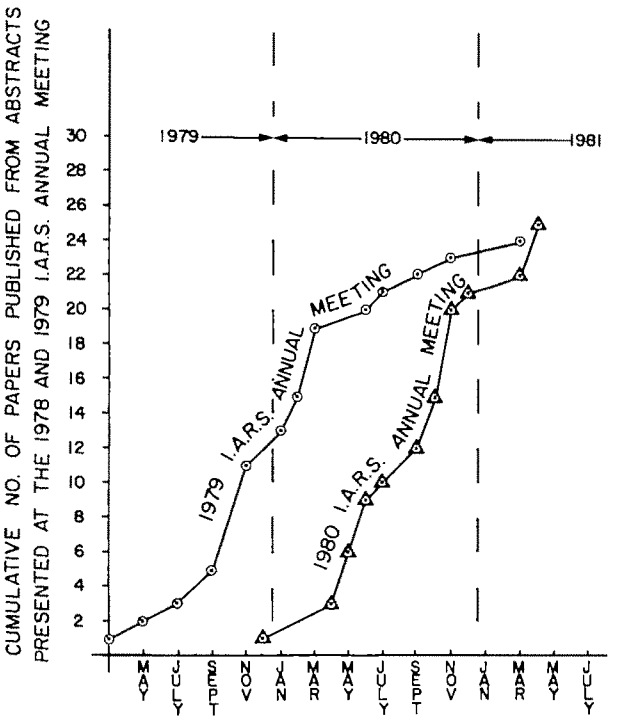


FIG 1. Cumulative number of papers appearing in peer-reviewed journals over a 27-month period following abstract presentation at the 1979 annual meeting and over a 15-month period following presentation at the 1980 annual meeting of the International Anesthesia Research Society (I.A.R.S.). Most papers so derived appeared between 6 and 24 months after abstract presentation.

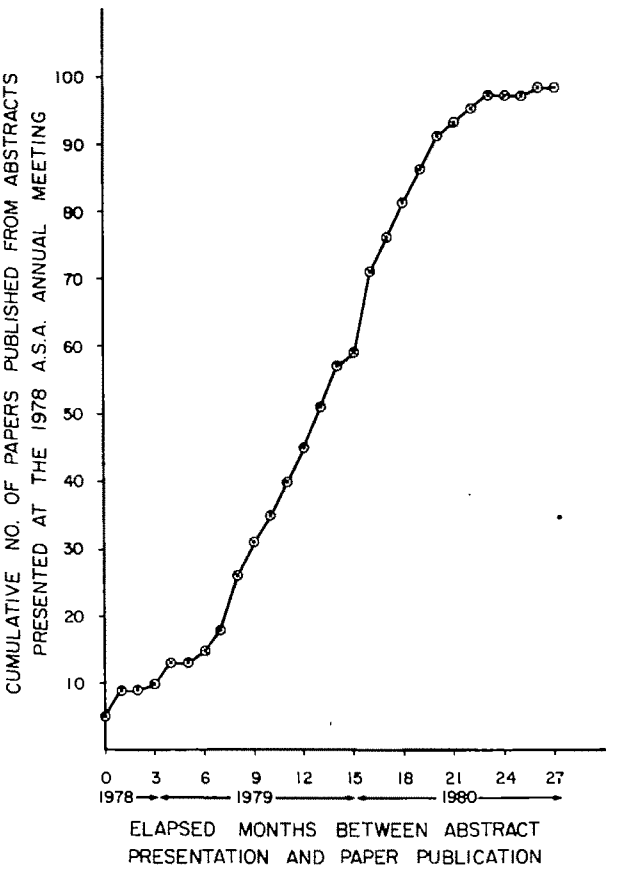


FIG 2. Cumulative number of papers appearing in peer-reviewed journals over a 27-month period following presentation of abstract from which paper was derived at the 1978 annual meeting of the American Society of Anesthesiologists (A.S.A.).

Index (SCI), was used to determine the number of times each abstract was cited and a similar division into anesthesia and nonanesthesia journals was accomplished. The inclusive dates for this search were 1977 to 1981.

Results

Twenty-four papers have resulted from 55 abstracts (43.6%) presented at the 1979 annual meeting and 25 papers from 62 abstracts (40.3%) presented at the 1980 annual meeting of the I.A.R.S. Ninety-eight papers have resulted from 100 of the 324 abstracts (31.1%) presented at the 1978 annual meeting of the A.S.A. The average time for publication was 8.2 months for the I.A.R.S. abstracts and 12.5 months for the A.S.A. abstracts. For both meetings, papers were most likely to appear between 6 and 19 months following presentation as abstracts (Figs 1 and 2). Although the majority of papers were published in anesthesia journals, the rest of the papers appeared in a wide variety of basic science and clinical journals (Table).

Discussion

Publications

There are various reasons why an abstract is not followed by a formal paper. Discussions following abstract presentation may suggest errors in design or methodology. In fact, Relman (1) has pointed out that abstract presentations are intended not merely to convey information, but to elicit criticism and suggestions. Other reasons for nonpublication of an abstract include: insufficient data collection or unfavorable manuscript review.

Our search methods, using the name of the individual presenting the abstract, assured that we would not miss any papers as the individual presenting the abstract would surely be one of the authors of the formal paper. When the author is known, an author search is the most expedient way of locating published papers. For that reason no further search using MEDLARS key words and subject headings was made (2).

TABLE

Papers Derived from 1978 American Society of Anesthesiologists (A.S.A.) Abstracts and from 1979 and 1980 International Anesthesia Research Society (I.A.R.S.) Abstracts

	1978 A.S.A.		1979 I.A.R.S.		1980 I.A.R.S.	
	No.	Months*	No.	Months*	No.	Months*
Anesthesia journals						
Acta Anaesthesiol Scand	1	8	0	0	1	4
Anaesthesia	0	0	0	0	1	7
Anaesthesist	1	15	0	0	0	0
Anesth Analg	19	11.6	13	10.8	12	6.3
Anesthesiology	36	13.7	1	13	6	9.8
Br J Anaesth	2	3.5	0	0	0	0
Can Anaesth Soc J	7	16.1	5	10	0	0
Masui	0	0	1	9	0	0
Anesthesia subtotals	66	12.4	20	8.6	20	7.3
Nonanesthesia journals						
Am J Physiol	1	18	0	0	0	0
Ann Intern Med	1	9	0	0	0	0
Arch Surg	1	21	1	17	0	0
Biochem Pharmacol	1	5	0	0	0	0
Biochim Biophys Acta	1	7	0	0	0	0
Biol Neonate	1	9	0	0	0	0
Chest	2	10	0	0	0	0
Circ Shock	1	9	0	0	0	0
Circulation	1	14	0	0	0	0
Crit Care Med	2	15	0	0	1	5
Drug Metab Rev	1	13	0	0	0	0
J Am Vet Med Assoc	0	0	0	0	1	9
J Appl Physiol	4	12.3	1	16	0	0
J Cardiovasc Pharmacol	1	15	0	0	0	0
J Chromatogr	1	12	0	0	0	0
J Pharmacol Exp Ther	6	7.5	1	9	1	9
J Thorac Cardiovasc Surg	4	15.8	1	9	0	0
JAMA	1	16	0	0	0	0
Pain	0	0	0	0	1	8
Radiology	1	0	0	0	0	0
Trans Am Neurol Assoc	0	0	0	0	1	0
Nonanesthesia subtotals	31	11.3	4	12.3	5	6.2
Grand totals	97	12.2	24	9.3	25	7.1

* Average time between meeting and publication of paper.

Abstracts submitted for presentation at annual meetings are reviewed by individuals who are unaware of the origin of the abstract. However, their examination of the data and scrutiny of the methods cannot be as rigorous or as effective as that applied to papers published in most scientific journals. The abstract reviewers are working under the pressure of an inflexible deadline and they cannot suggest modifications. They must accept or reject the abstract without qualification. Furthermore, an abstract usually does not contain sufficient detail to allow the full evaluation of originality, validity, and significance that a final article does. Therefore, because of constraints of time and space, the reviewer of an abstract may not have enough information to make a decision with the accuracy that the reviewer of an article is afforded. Therefore, the review process at best is less than that which a manuscript submitted to a peer-reviewed journal is likely to receive. Thus, data contained in such an abstract must be considered as preliminary until passing more stringent peer review. For this reason, caution is recommended in accepting such abstract data and in citing abstracts as references (3).

Abstract Citation

In an analysis of the fate of cardiology research abstracts, Goldman and Loscalzo (3) pointed out that

prospective authors have been advised to "try to avoid using abstracts as references." A survey of the section "Information for Authors" from six major anesthesia journals provided no consistent policy regarding abstract citation. *Anesthesia and Analgesia* advises the avoidance of abstract citation. *Anesthesiology* specifies that "only indexed abstracts published within the last 4 years are acceptable." Neither the *Canadian Anaesthetists Society Journal, British Journal of Anaesthesia, Acta Anaesthesiologica Scandinavica,* nor *Anaesthesist,* include a specific statement on abstracts.

However, the most current and pertinent data bearing on a given subject may well be available only in a published abstract. The lag time between abstract presentation and publication of the paper derived from the abstract varies greatly. This population of abstracts suggests that most of these papers will be published within 24 months. Similar data have been noted previously in nonanesthesia fields (3, 4). The likelihood that a paper will result from a given abstract more than 4 years after presentation is remote. Therefore, failure to have the scientific validity of the abstract data reaffirmed by publication in a peer-reviewed journal after a 36- to 48-month period appears to be reasonable and conservative.

By July 1, 1981, four 1980 I.A.R.S. abstracts appeared as citations in Science Citation Index. Only one of the four cited abstracts was later published as a paper. By January 1, 1981, fifty-six 1979 A.S.A. abstracts had been cited, and 21 of the 56 cited abstracts were subsequently published as papers.

Although publication of abstracts has made them available to all investigators (and not just those attending the annual meeting), the citation rate may, in part, reflect editors' acceptability of indexed abstracts.

In conclusion, 24 of 55 (43.6%) 1979 I.A.R.S. annual meeting abstracts, 25 of 62 (40.3%) 1980 I.A.R.S. annual meeting abstracts, and 100 of 324 (30.1%) 1978 A.S.A. annual meeting abstracts resulted in 97 publications by the cut-off dates of July 1, 1981 for the I.A.R.S. papers and January 1, 1981 for the A.S.A. papers. Most papers were published in anesthesia journals, but a variety of other disciplines were also represented. The average lag time between presentation and publication was 8.2 months for the I.A.R.S. and 12.2 months for the A.S.A. abstracts. The change in the practice of publication of abstracts for both societies between 1978 and 1979 has resulted in greater citation frequency, presumably related to improved accessibility to investigators and acceptability to editors.

REFERENCES

1. Relman AS. News reports of medical meetings: how reliable are abstracts? N Engl J Med 1980;303:277–8.
2. Meranze J, Ellison N, Greenhow DE. Publication of 1978 A.S.A. abstracts. Anesthesiology 1981;51:A-350.
3. Goldman L, Loscalzo A. Fate of cardiology research originally published in abstract form. N Engl J Med 1981;303:255–9.
4. Dudley HAF Surgical research: master or servant? Am J Surg 1978;135:358–60.

REVIEW
article

Transcutaneous Electrical Nerve Stimulation: An Alternative Approach to the Management of Postoperative Pain

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THE MANAGEMENT of postoperative pain has been and continues to be a significant problem in surgical practice in terms of both the additional stress it places on the patient's physiologic reserves and the symptomatic discomfort it causes. It is well known by practitioners that pain is an individual experience and this fact is reflected in a wide variation in the incidence and severity of pain and in the need for analgesics. A number of factors including age, anesthetic technique, personality of the patient, previous experience, physical status, site of operation, and surgical management affect the incidence of postoperative pain (1, 2).

In light of the problems associated with postoperative pain, various strategies for the management of pain have been proposed. The most commonly used method stresses the use of systemic analgesics, narcotics, and related drugs. Regional analgesia offers an attractive alternative to the use of narcotics and tranquilizers in that respiratory depression and sedation are avoided and the patient can be made pain free for extended periods using long-acting local anesthetics. Regional analgesia is not without problems, however, and its use requires the presence of an anesthesiologist who is skilled in regional block techniques and who is prepared to treat the occasional complication that may develop. Recently, the use of epidural morphine has been advocated for the treatment of postoperative pain (3). The advantages of epidural morphine included prolonged analgesia and lack of sympathetic or motor block. Unfortunately, epidural morphine also has its disadvantages. Generalized itching, urinary retention, respiratory depression, and respiratory arrest occurring up to 10 hours after injection have been reported (4, 5).

Within the last decade, there have been a small but increasing number of reports concerning the use of transcutaneous electrical nerve stimulation (TENS) for the relief of postoperative pain. This paper presents a review of these reports.

History

Historically, the use of electrical analgesia is an ancient technique. Electrical fish were first used to provide electricity for pain relief (6–8). The torpedo fish or electric ray, which is capable of emiting 200 V, was used by Greek and Roman physicians in the treatment of gout, headaches, and other ailments as far back as 46 AD. This method apparently involved bringing the patient's affected part into contact with the enraged fish, which was contained in a bucket of water. Indeed, electrical stimulation was sporadically used in the 17th and 19th centuries. Its use was

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Received from the Department of Anesthesiology and University of North Carolina Pain Clinic, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina; and the Department of Anesthesia, University of Pennsylvania, Philadelphia, Pennsylvania. Accepted for publication January 5, 1982.

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limited, however, by the technology of the time and overshadowed by simultaneous advances in the pharmacologic treatment of pain (7). Only recently have developments in the fields of electronics and neurophysiology allowed the development and clinical application of safe, reliable, and portable electrical stimulating devices.

Initially, TENS was introduced as a screening procedure to determine which patients were suitable for surgical placement of dorsal column stimulators for pain relief. Although unsuccessful in this application, it was noted that TENS produced local analgesia and that it might be useful therapeutically in and of itself in patients with chronic pain.

There are now sufficient studies available in the literature to assess the value of TENS in the treatment of both chronic and acute pain. Externally applied electrical stimulation is now in common use in most pain treatment programs and is gradually gaining acceptance in the treatment of postoperative pain.

Theory

The use of afferent stimulation techniques, often called neuromodulation, is based on application of the gate control theory of pain originally advanced by Melzack and Wall (9) in 1965. Briefly, the gate control theory postulates that impulse transmission from afferent nerve fibers to the spinal cord transmission cells is modulated by a spinal gating mechanism in the substantia gelatinosa. The relative amounts of activity in the large myelinated A-beta fibers and small A-delta and C fibers influence the gating mechanism in a way such that large fiber activity inhibits transmission (closes the gate) while small fiber activity facilitates transmission (opens the gate). In addition, a central biasing mechanism receives information over a rapidly conducting large fiber system and further modulates the gating mechanism via descending fibers, thus allowing cognitive processes to influence pain perception.

The rationale for the use of electrical stimulation to produce analgesia is based upon the premise that stimulation of large peripheral nerve fibers closes the spinal gate and thus prevents painful peripheral stimuli from gaining access to the ascending transmission system. In support of this theory is the observation that large myelinated fibers have a low threshold to electrical stimulation (10). TENS is believed to inhibit the relay of painful stimuli by causing a series of impulses to be conducted through the large fibers.

An alternative explanation for the ability of TENS to produce analgesia is based upon the premise that stimulation causes release of endorphins which subsequently attach to receptors and inhibit transmission of noxious stimuli. The neurophysiologic basic of this explanation rests on several pieces of evidence. First, opiate receptors have been identified in the substantia gelatinosa (the proposed site of the spinal gating mechanism) and in the periaqueductal gray matter of the brain (the proposed site of the central control trigger) (11). Second, Solomon et al (12), in looking at the effectiveness of TENS in decreasing postoperative pain and narcotic requirements, found that although TENS was effective in reducing pain and narcotic requirements in patients without a history of previous narcotic use, it was ineffective in patients with a history of narcotic use for a period greater than 2 months during the 6 months before surgery. These same patients also reported little or no relief from large amounts of narcotic analgesics. This suggests that the mechanism of action of electrical analgesia may involve the same neural substrate as narcotic-induced analgesia. This hypothesis may also explain why brief periods of stimulation can produce prolonged periods of pain relief. However, recent work by Abram et al (13) in patients with chronic pain fails to support this hypothesis. In their study, 15 patients who had been using transcutaneous electrical stimulation successfully for at least 1 month were given intravenous injections of naloxone (0.4 or 1.2 mg) or saline in a double-blind fashion in an attempt to reverse the stimulation-induced analgesia. No reversal of analgesia was seen after administration of naloxone or saline, suggesting that transcutaneous stimulation under the conditions used (low intensity 58 Hz stimulus) was not associated with release of endogenous opiates.

Melzack (14) recently offered a more generalized hypothesis to explain the analgesic effect produced by brief, intense peripheral stimulation. According to this theory, cells in the central gray matter have large receptive fields and complex projections. The arrival of peripheral impulses in this area results in perception of the stimulus but also activates inhibitory fibers in the brainstem which block painful stimuli from other body parts. Thus, TENS may activate inhibitory reflex areas in the brainstem.

Clinical Use of TENS

Regardless of the mechanism of action of TENS, TENS has assumed an important role in the management of chronic pain. More recently a number of investigators have studied the efficacy of TENS in the management of acute postoperative pain. The first

reported use of TENS for postoperative pain relief was by Hymes et al (15) in 1974. In this study, 115 patients were stimulated either continuously or intermittently for 4 of 5 days after surgery. Patients who were stimulated reported an 80% reduction in the intensity of pain. A curious exception was noted in patients having splenectomy or nephrectomy: only two of 16 patients reported pain relief following treatment. The authors also reported a significant decrease in the incidence of postoperative atelectasis and ileus as well as reduction of 1½ days in the average length of stay in the postoperative intensive care unit. A major defect in this study was the authors' choice of control patients. Although the control population did not differ in sex, age, type of surgery, or surgeons performing the procedure, control patients were chosen retrospectively from patients who had had operations 2½ years before the onset of the study. This absence of concurrent control patients raised questions about the validity of the findings of the study, as well as the possibility that patients in the experimental group had a placebo response from the stimulator.

In a prospective, randomized controlled study by Cooperman et al (16), 50 patients had stimulators with or without current applied after upper abdominal surgery. If pain was not relieved by the stimulator, the patient was given 10 mg of diazepam. If this failed to provide adequate pain relief, 75 to 100 mg of meperidine was given. This procedure was repeated for 5 days each time the patient complained of pain. Good to excellent results (defined as a requirement of less than three doses of meperidine in 24 hours) were reported in 77% of patients with functioning stimulators. In contrast, only 33% of patients who had stimulators without current reported good to excellent results. Of patients with active stimulators 35% required no additional analgesia after surgery compared with 12% in the control group. There was, however, no difference between the two groups of patients in the incidence of postoperative atalectasis or pneumonia, in the duration of postoperative ileus, or in the length of stay in the postoperative intensive care unit. In addition, patients with malignant diseases did not respond as well to TENS as did patients with benign diseases, a finding that suggests that anxiety may play an important role in limiting the effectiveness of TENS.

Rosenberg et al (17) studied 12 patients who had cholecystectomy. Six of the 12 had TENS. Six control patients were given meperidine on demand, as were the patients given TENS. The results showed a 3-fold reduction in narcotic requirement in patients receiving TENS. Despite this difference, respiratory function as measured by arterial blood gas tensions, maximum expiratory flow rate, forced expiratory volume after 1 second, and vital capacity were not significantly different in the two groups. In addition, there was no difference in the incidence of postoperative atalectasis or the duration of ileus.

A number of studies show TENS to be effective in managing postoperative pain and reducing narcotic requirements. In a well controlled study by VanderArk and McGrath[18] TENS was found to be effective in alleviating acute postoperative pain in 67 patients in comparison with a control group of 39 patients who were given the same instructions before surgery but were given stimulators without batteries. Patients were stimulated or had placebo stimulation for 20 minutes three times per day until the day of discharge. In patients with functioning stimulators, 25% obtained complete relief of pain and required no narcotics after surgery, 52% obtained partial relief and required small doses of narcotics, and 23% had no relief. In contrast, only 17% of the control patients obtained partial relief whereas the remaining 83% obtained no relief. A small number of patients who were stimulated reported decreasing efficacy as the novelty of the therapy diminished, a finding that perhaps indicates a placebo effect.

A few remarks about the patients used in the control group in this study are pertinent. VanderArk and McGrath were the first investigators who advocated no battery or no current controls. The patients were informed that they might or might not perceive a tingling sensation in the area where the electrodes were in contact with the skin and were assured that pain medication would be available if the TENS did not relieve the pain. Although patients were not told to equate tingling with pain relief, it is certainly possible that the presence or absence of tingling could have affected the patient's perception of the effectiveness of TENS. This same problem of finding suitable control patients in the study of TENS continues to trouble investigators. Melzack (14) has advocated using the placebo Venagus wave in control subjects. Subjects are told that they will receive a high frequency Venagus wave (named after the engineer who developed the equipment) which is known to abolish pain. All stimulating conditions are the same as those experienced by test subjects including wave forms on an oscilloscope and flashing lights on the stimulator. However, an open switch prevents any current from stimulating the subjects' skin. The validity of no

battery or no current controls has yet to be determined, but, until a better method is found, it is likely that its use will continue.

Stabile and Mallory (19) used TENS for postoperative pain relief in a prospective, randomized study of patients undergoing total hip replacement or total knee replacement. Patients in this study were divided into three groups: group 1 consisted of 42 patients given hydromorphone intramuscularly for pain relief; group 2 consisted of 43 patients who received TENS plus hydromorphone on request; group 3 consisted of 22 patients who were given nerve stimulators without batteries plus hydromorphone on request. The results showed that patients in both groups 2 and 3 required significantly less postoperative narcotics than did patients in group 1 during the first three postoperative days. A positive placebo effect was noted in group 3, suggesting that the psychological benefits gained by allowing the patient to participate in his pain management and the relief of preexisting anxiety that results from exposure to electronic gadgetry which the patient believes will have an effect on postoperative pain may influence the patient's response to postoperative pain.

The use of TENS in the rehabilitation of patients is considered to be a major advance in the control of postoperative knee pain. Harvie (20) used TENS after surgery in 34 patients who had total knee replacements, synovectomies, meniscectomies, knee arthrotomies, patella plasties, or open reduction of fractures about the knee joint. Stimulation was applied as soon as the patient was fully recovered from the anesthetic and the patient controlled the unit for a period of 4 to 7 days. Quadriceps and range of motion exercises were also used. Electrode placement over the medial and collateral ligaments was found to produce a better response than electrodes placed on the medial sides of the incision. The decrease in the use of narcotics associated with TENS ranged from 75% to 100%. Five patients did not require any narcotics in the immediate postoperative period. When TENS was used, improvements were also noted in straight leg raising and range of motion exercises, together with a decrease in the length of hospital stay.

In a study of Pike (21), TENS was used for management of pain in 20 patients undergoing total hip replacement. The control group in this study received only narcotics for postoperative pain. The patients who were stimulated were also allowed to request 30 mg of meperidine on demand for pain. The stimulation was applied either intermittently or continuously and was discontinued 8 hours after surgery. Patients receiving TENS required 1.3 ± 1.38 (SD) doses of meperidine during the first 24 hours following surgery whereas control patients required 4.3 ± 2.05 doses. The difference was statistically significant.

In a study by Schuster and Infante (22), TENS was used in the management of postoperative pain for 72 hours following low back operations in 26 patients. The control group of 26 patients received only narcotics for postoperative pain. Patients receiving TENS also received narcotics on demand for pain. Patients in the TENS group required 4.65 ± 3.66 doses of narcotic compared with 10.92 ± 6.17 doses in the control group. The difference was statistically significant.

Finally, in a well controlled, prospective study by Ali et al (23), TENS was used in patients undergoing elective cholecystectomy. This study was designed to examine the efficacy of TENS in relieving postoperative pain and to evaluate the effect TENS had on postoperative pulmonary function. Patients with pulmonary disease were excluded from the study and apart from the use of TENS, postoperative care was standardized. All patients were required to do deep breathing, coughing, turning, and leg exercises; all patients were ambulated at 24 hours. Analgesia for the first 72 hours after surgery was restricted to meperidine, 1.5 mg/kg, on demand. The patients were divided into three groups: group 1 consisted of 15 patients who received TENS plus meperidine; group 2 consisted of 15 patients who received meperidine only; and group 3 consisted of 10 patients who received stimulators without current plus meperidine. Assessment of postoperative pulmonary function was done by measuring arterial P_{O_2}, vital capacity, and functional residual capacity 4 to 8 hours after surgery and again on postoperative days 1, 3, and 5. Patients receiving TENS required meperidine with a frequency of 4.7 ± 2.5 doses whereas those in groups 2 and 3 required 10.1 ± 2.7 and 10.4 ± 2.7 doses, respectively. Arterial P_{O_2}, vital capacity, and functional residual capacity decreased after surgery in all groups. In the TENS group, vital capacity decreased to 58.8% ± 10.6% of the preoperative value on the day of surgery whereas functional residual capacity decreased to 76.7% ± 12.3% and arterial P_{O_2} to 93.1 ± 5.6% of preoperative values. All measurements in the TENS group improved in the postoperative period so that by day 5 the values had nearly returned to preoperative values. Corresponding changes in group 2 showed a decrease in vital capacity to 31.2% ± 5.9%, a decrease in functional residual capacity to 61.9% ± 13.4%, and a decrease in arterial P_{O_2} to 78% ± 6.8% of preopera-

tive values. Corresponding changes in group 3 showed a decrease in vital capacity to 29% ± 4.2%, a decrease in functional residual capacity to 64.2% ± 13.1%, and a decrease in arterial P_{O_2} to 75.2% ± 6.0% of preoperative values. Although serial measurements in groups 2 and 3 showed improvement over the study period, the values obtained on postoperative day 5 remained significantly lower than those seen in patients receiving TENS. In addition, six pulmonary complications consisting of one case of lobar pneumonia and five cases of lower lobe atelectasis were seen in groups 2 and 3. No postoperative pulmonary complications were noted in patients given TENS.

In a study unrelated to postoperative pain relief, Perdkis (8) used TENS to treat 20 cases of protracted ileus resulting from abdominal surgery or trauma. Therapy was started 5 to 12 days after conservative treatment for ileus had failed. In 16 patients, ileus was completely relieved within 24 hours. Three cases did not improve with TENS therapy but were found to have mechanical obstruction at laparotomy. Because no control patients were used in this study, it is difficult to draw conclusions regarding the efficacy of treatment as the frequency with which ileus would have resolved spontaneously is unknown.

Practical Considerations

More than 200 companies in the United States now manufacture TENS devices for the relief of acute and chronic pain. There are no industry-wide standards, however, and it is possible that some of the discrepancies in the effectiveness of TENS noted in the previously cited studies may be related to differences in stimulator current properties.

Most stimulators in current clinical use deliver a balanced, biphasic potential in either a square or spiked wave form. Biphasic wave forms are used to prevent iontophoresis (i.e., transfer of ions from the skin to the TENS unit and vice versa). In addition, the wave forms may be either symmetrical or asymmetrical in configuration. Regardless of the configuration, it is important that the current be delivered equally in both phases of the wave to prevent electrolysis in the skin. Most commercially available TENS units utilize the asymmetric wave form primarily because this wave form has been found to be more acceptable to patients in terms of comfort and lack of muscle contractions (a nuisance commonly seen with symmetric wave forms at low stimulus frequencies).

The ideal pulse width is in the range of 60 to 150 μsec. Below this range, the amplitude of the stimulating current must be increased to obtain satisfactory results. This leads to rapid exhaustion of the stimulator power supply. Above 200 μsec, the current stimulates motor fibers to peripheral muscle resulting in muscle contraction.

The frequency at which the electrical current is delivered by the stimulator is a matter of controversy. Most TENS units are capable of delivering a range of stimuli from 10 to 100 Hz. There appears to be a strong patient preference for pulse frequencies greater than 50 Hz and most investigators feel that high frequency (80 to 100 Hz), low intensity stimulation gives the best results in the treatment of postoperative pain. The current amplitude is initially set before surgery by the patient who finds a point that produces analgesia and which is just below the threshold of discomfort or motor stimulation (approximately 12 to 20 mamp), by a trial and error method. The sensation produced is described as tingling, vibrating, or soothing and is usually effective within a few minutes after stimulation has begun.

In the operating room immediately after skin closure, sterile pregelled electrodes are applied to the skin on either side of the incision approximately 1.0 cm away from the suture line. Sterile dressings are then taped into place. As the patient is extubated, the electrodes are connected to a battery-operated stimulus generator and the current is adjusted to a level determined in the preoperative period. After the patient is fully awake, the current is reset to a subjectively comfortable level in the recovery room. The electrodes are left in place and continuous stimulation is administered for 48 to 72 hours after surgery. Mobilization of the patient does not interfere with its efficacy. Analgesic effect lingers for hours and occasionally prolonged analgesia may follow brief periods of stimulation.

Other investigators, however, favor the use of low frequency (2 to 5 Hz), high intensity stimulation. It is believed that this type of stimulation causes release of endorphins (24, 25), and, in fact, some patients with chronic pain appear to respond more favorably to this mode of stimulation. At the present time, low frequency stimulation is primarily used in electroacupuncture and has yet to be studied for the relief of postoperative pain. Low frequency stimulation has several disadvantages. These include latency of onset of up to 20 minutes following initial stimulation and the fact that the high intensity currents used can be quite uncomfortable.

It is not clear whether stimulus frequency or intensity is the critical factor in activating endorphin mech-

anisms. Analgesic effects of low frequency, low intensity currents have not been reported and high frequency, high intensity stimulation is not tolerable to patients. As noted earlier, the analgesic effect of high frequency, low intensity TENS is not related to endorphin release as evidenced by the failure of naloxone to reverse TENS-induced analgesia (13).

Finally, electrode placement may also influence the efficacy of TENS. Harvie (20) has reported that placement of electrodes over the medial and collateral ligaments of the knee gave better results than placement on the sides of the incision. Mannheimer (26) suggests that multiple electrode placement in areas of diffuse pain or placement in a parallel or crossed pattern in a specific anatomic site may be most beneficial.

No complications have been observed from TENS when used properly, and the only morbidity has involved skin reactions at the electrode sites. Contraindications to the use of TENS include demand cardiac pacemakers and the first trimester of pregnancy (27).

Discussion

The use of TENS appears to offer a number of advantages in the treatment of postoperative pain. The problems of respiratory depression, sedation, orthostatic hypotension, and urinary retention seen with narcotics are avoided or reduced. The method is simple, noninvasive, nontoxic, and continuous. Physiologic or psychologic dependence does not develop with the use of TENS. There is a high level of patient acceptance and some physicians have noted that TENS enhances the physician-patient relationship by the extra concern for patient welfare and comfort that is shown when TENS is used.

The above studies indicate that TENS is often effective in relieving postoperative pain and reducing narcotic requirements. In a small number of patients, the need for narcotic analgesia is eliminated altogether. As noted by a number of observers, TENS appears to be most effective in relieving pain caused by trauma to muscles, bones, or peripheral nerves. Poorly localized visceral pain is less likely to respond. Psychological factors may play an important role in the response to TENS and briefing the patient before surgery on the potential value of TENS as a method of pain relief may improve the results. TENS is less effective in anxious or depressed patients. Although a placebo effect cannot be ruled out as playing a role in the effectiveness of TENS (19), the fact that patients who use stimulators without current require more narcotic after surgery suggests that TENS is acting through neurophysiologic processes.

An issue that has not been commented on by any of the previously mentioned investigators is the cost-effectiveness of TENS. In our institution, the initial charge to the patient for applying a stimulator is $27.00. This includes the fee of the therapist and the cost of the stimulating electrodes. Subsequent daily visits by a therapist for maintenance of the unit cost $4.00/day. Assuming use of the stimulator for 4 days, the total charge to the patient is $39.00. In contrast, 10 mg of morphine costs $0.46 and 100 mg of meperidine costs $0.62. Assuming six doses of narcotics per day, the cost of 4 days of narcotics is $11.04 and $14.88 for morphine and meperidine, respectively. Therefore, the use of TENS appears to be at least 3 to 4 times more costly than conventional therapy with narcotics in the management of postoperative pain. On the other hand, if TENS does decrease postoperative morbidity, as suggested by a number of authors, its use may actually decrease the overall cost of postoperative management, including a shorter duration of hospitalization. Just as important as the comparison of the costs of TENS and narcotic therapy is the question of which patients should use TENS. As alluded to earlier in this review, not all patients have significant pain after surgery. Should every patient receive TENS on completion of surgery or should its use be restricted to a more select population that has yet to be defined? Routine use of TENS would undoubtedly increase the cost of hospitalization which in certain cases might not be necessary as not all patients have severe enough postoperative pain to warrant the use of TENS. Enthusiasts of the use of TENS, however, frequently point to the claims made in the early work of Hymes et al (15) that TENS reduces the incidence of postoperative atelectasis, duration of ileus, and length of stay in a postoperative intensive care unit and that it should therefore reduce the cost of surgery and hospitalization. Subsequent studies by Cooperman et al (16) and Rosenberg et al (17) fail to support these claims. More recent work by Harvie (20) suggests, on the other hand, that for patients undergoing operations on the knee, TENS may be particularly indicated in view of the significant improvement in range of motion in the affected part and a decreased length of time spent in the hospital. Furthermore, Ali et al (23) suggest that TENS reduces postoperative pulmonary morbidity and improves postoperative pulmonary function by modifying the pain-induced decreases in vital capacity, functional residual capacity, and arterial oxygen tension.

Given this information and the problem of cost-effectiveness of a new treatment modality, which patients are most likely to benefit from TENS? The available data indicate that TENS is especially effective in modifying pain related to musculoskeletal trauma. Patients undergoing knee, hip, and low back surgery require less postoperative narcotics, are able to ambulate earlier with less pain, and may spend less time in the hospital. Although conflicting claims have been made, TENS appears to be effective in reducing the incidence of postoperative pulmonary complications in patients without preexisting lung disease. Whether TENS is equally useful in patients with chronic lung disease is a question that has yet to be answered, although, given the data by Ali et al (23) postoperative pulmonary function might be less adversely affected by TENS than by use of systemically administered narcotics. Another group of patients who might derive special potential benefit from the use of TENS are geriatric patients who are, in many cases, particularly sensitive to the side effects of depressant medications.

The use of TENS is attractive from the point of view that it not only has no known side effects but also that it is effective in the majority of patients in modifying or eliminating postoperative pain. As with all new modes of therapy, the cost of the devices used in TENS is high and, although we conclude that TENS is of considerable value in the reduction of postoperative pain and certainly deserves further clinical trials, it is currently only an adjunct to more classic pharmacologic methods of pain relief. In terms of patient acceptance, nursing care, and functional results, TENS has advantages over alternative analgesic regimens. Its future in the postoperative management of pain will depend, first, on establishment of its cost-effectiveness and, second, on more precise definition of exactly what types of patients will benefit more from TENS than from reliance on conventional pharmacologic means for the relief of postoperative pain.

With regard to technical standards and the electrical characteristics of the current that should be used in the treatment of postoperative pain, there is little agreement among the experts. Most of the investigators referred to in this article have used stimulator settings specified by the manufacturers of the respective units. In general, the most satisfactory results have been obtained utilizing stimulators that deliver a high frequency (50 to 100 Hz), low intensity (12 to 20 mamp at 1000 ohm) current with an asymmetric, biphasic wave form. These stimulators are comfortable to use and readily accepted by the patients. Although there is little specific information regarding which current parameters are most efficacious, most investigators agree on a positive outcome in the treatment of postoperative pain differing only on the frequency and duration of success. This fact suggests that the different current characteristics associated with various commercially available stimulators are important only in that they should fall within the general guidelines mentioned above in order to obtain a reasonable rate of success. Any further recommendations regarding the technical aspects of TENS current must await future studies looking specifically at various frequencies, wave forms, and current intensities.

REFERENCES

1. Loan W, Morrison J. The incidence and severity of postoperative pain. Br J Anaesth 1967;39:695–8.
2. Parkhouse J, Lambrechts W, Simpson B. The incidence of postoperative pain. Br J Anaesth 1961;33:345–53.
3. Bromage P, Camparesi E, Chestnut D. Epidural narcotics for postoperative analgesia. Anesth Analg 1980;50:473–80.
4. Christensen V. Respiratory depression after extradural morphine. Br J Anaesth 1980;52:841.
5. Davis G, Tolhurst-Cleaver C, James T. CNS depression from intrathecal morphine. Anesthesiology 1980;52:280.
6. Kellaway P. The past played by electrical fish in the early history of bioelectricity and electrotherapy. Bull Hist Med 1946;20:112–37.
7. Kane K, Taub A. A history of local electrical analgesia. Pain 1975;1:125–40.
8. Perdkis P. Transcutaneous nerve stimulation in the treatment of protracted ileus. S Afr J Surg 1977;15:81–6.
9. Melzack R, Wall PD. Pain mechanisms, a new theory. Science 1965;150:971–9.
10. Bloedel J, McCreery D. Organization of peripheral and central pain pathways. Surg Neurol 1975;4:65–81.
11. Snyder SH. Opiate receptors in the brain. N Engl J Med 1977;296:266–71.
12. Solomon R, Viernstein M, Long D. Reduction of postoperative pain and narcotic use by transcutaneous electrical nerve stimulation. Surgery 1980;87:142–6.
13. Abram S, Reynolds A, Cusick J. Failure of naloxone to reverse analgesia from transcutaneous electrical stimulation in patients with chronic pain. Anesth Analg 1981;60:81–4.
14. Melzack R. Prolonged relief of pain by brief, intense, transcutaneous somatic stimulation. Pain 1975;1:357–73.
15. Hymes A, Raab D, Yonehiro E, Nelson G, Printy A. Acute pain control by electrostimulation: a preliminary report. Adv Neurol 1974;4:761–7.
16. Cooperman A, Hall B, Mikalacki K, Hardy R, Sadar E. Use of transcutaneous electrical stimulation in the control of postoperative pain. Am J Surg 1977;133:185–7.
17. Rosenberg M, Curtis L, Bourke. Transcutaneous electrical nerve stimulation for the relief of postoperative pain. Pain 1978;5:129–33.
18. VanderArk G, McGrath K. Transcutaneous electrical stimulation in treatment of postoperative pain. Am J Surg 1975;130:338–40.
19. Stabile M, Mallory T. The management of postoperative pain in total joint replacement: transcutaneous electrical nerve stimulation is evaluated in total hip and knee patients. Orthopaedic Rev 1978;7:121–3.
20. Harvie KW. A major advance in the control of postoperative knee pain. Orthopedics 1979;2:26–7.

21. Pike PMH. Transcutaneous electrical stimulation: its use in the management of postoperative pain. Anaesthesia 1978;33:165–71.
22. Schuster G, Infante M. Pain relief after low back surgery: the efficacy of transcutaneous electrical nerve stimulation. Pain 1980;8:299–302.
23. Ali J, Yaffe C, Senette C. The effect of transcutaneous electric nerve stimulation on postoperative pain and pulmonary function. Surgery 1981;89:507–12.
24. Sjolund B, Terenius L, Erikson M. Increased cerebrospinal fluid levels of endorphins after electroacupuncture. Acta Physiol Scand 1977;100:382–4.
25. Chapman RN, Benedett, C. Analgesia following transcutaneous electrical stimulation and its partial reversal by a narcotic antagonist. Life Sci 1977;21:1645–8.
26. Mannheimer JS. Electrode placement for transcutaneous electrical nerve stimulation. Phys. Ther., 1978;58:1455–62.
27. Burton C. Transcutaneous electrical nerve stimulation to relieve pain. Postgrad Med 1976;59:105–8.

Reduced Stress Response with Pulsatile Flow during Cardiopulmonary Bypass

The effect of pulsatile flow during cardiopulmonary bypass on the hormonal stress response was studied in 26 patients. Thirteen patients had "routine" bypass and 13 had pulsatile bypass with an average pulse pressure of 30 mm Hg. Plasma vasopressin levels were significantly elevated during bypass in both groups, but were lower with pulsation (66 ± 11 vs 36.3 pg/ml, $p < 0.05$). Epinephrine levels increased in both groups during bypass, but were higher after bypass (1179 ± 448 vs 713 ± 140 pg/ml, $p < 0.05$) and in the recovery room (1428 ± 428 vs 699 ± 155 pg/ml, $p < 0.05$) in the nonpulsatile groups. The same response was noted in norepinephrine levels (924 ± 225 vs 465 ± 90 pg/ml, $p < 0.05$; 1915 ± 491 vs 717 ± 112 pg/ml, $p < 0.05$). There was no significant changes in renin activity in either group, but the increase after cardiopulmonary bypass was greater in the nonpulsatile group (2.0 ± 0.7 vs 1.36 ± 0.4 ng/ml/hr, NS). These data suggest that pulsatile flow significantly attenuates the vasopressin and catecholamine stress response to cardiopulmonary bypass. This may explain the increased flow requirements and better tissue perfusion and organ function and the decreased incidence of postoperative hypertension after bypass using pulsatile flow. (*Philbin DM, Levine FH, Kono K, et al. Attenuation of the stress response to cardiopulmonary bypass by the addition of pulsatile flow. Circulation 1981;64:808–12*)

technical
COMMUNICATION

Evaluation of an Isoflurane Vaporizer: The Cyprane Fortec

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STEFFEY, E. P., WOLINER, M., AND HOWLAND, D.: Evaluation of an isoflurane vaporizer: the Cyprane Fortec. Anesth Analg 1982;61:457–64.

The delivery performance of two Fortec vaporizers for isoflurane in oxygen (O_2) was evaluated. Isoflurane concentration was measured at a constant O_2 flow rate (from 0.75 to 15 L/min) as the vaporizer dial setting was changed over the range of 0% to 5%. At vaporizer dial settings of 2% or less the average delivered isoflurane concentration differed from dial settings by less than 0.25 vol% at all O_2 flows. At dial settings of 3% or greater delivered concentrations were greater than dial settings at O_2 flows less than 4 L/min and at O_2 flow greater than 4 L/min delivered were less than dialed concentrations. Time-related reductions in delivered concentrations were most evident at dial settings of 3% or greater and O_2 flow rates greater than 6 L/min. Increasing the environmental temperature to 30°C or decreasing it to 15°C increased or decreased, respectively, vaporized output when compared with conditions at 22°C. Little or no effect on vaporizer output was noted with simulated positive pressure ventilation up to a breathing circuit pressure of 25 torr. We conclude the Fortec vaporizer is as efficient in delivering isoflurane in O_2 as previous reports have shown the Fluotec Mark III to be in its delivery of halothane.

Key Words: ANESTHETICS, Volatile: isoflurane; EQUIPMENT: vaporizers.

Isoflurane (Forane) has recently been approved for general clinical use as an inhalation anesthetic. The purpose of this study was to evaluate the accuracy and stability of isoflurane delivery from a precision vaporizer specifically designed for isoflurane delivery: the Cyprane Fortec (Fraser Harlake, Inc., Orchard Park, NY).

Methods

The performance of two Fortec vaporizers was studied. Oxygen (O_2), at a constant driving pressure of 50 psi was the anesthetic carrier gas. A precision rotometer calibrated for O_2 (Matheson Gas Products) was used to ensure accuracy of carrier gas flow rate to the vaporizers. Room temperature was maintained at 22 ± 1°C as monitored by a Bureau of Standards thermometer positioned within 20 cm of the vaporizer. One vaporizer had approximately 30 hours of isoflurane delivery use before these studies and the other, recently received new from the manufacturer, was unused before these studies.

The outlet of the vaporizer was connected to a T-piece and tubing. Gas was obtained from the T-piece by hand sampling or via a vacuum pump (200 ml/min) positioned downstream from the gas analyzer. The sampling site was 20 cm distal to the vaporizer outlet. Isoflurane concentrations were determined at ambient pressure using a calibrated Beckman LB2 anesthetic analyzer. Calibrations were performed using certified isoflurane in nitrogen standards obtained from Matheson Gas Products and known isoflurane concentrations in air and O_2 prepared in our laboratory. There were no discrepancies of concern between calibration gas sources and carrier gas content.

To prepare laboratory standards, measured amounts of liquid isoflurane were added to a corked glass flask with a Hamilton microliter syringe (1). The internal volume of the flask had previously been determined by water displacement. Subambient pressure was created in the flask before adding liquid isoflurane. After adding the liquid anesthetic and allowing sufficient time for vaporization, the flask was equilibrated to barometric pressure with air or

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Received from the Department of Surgery, School of Veterinary Medicine, University of California, Davis, California 95616. Accepted for publication December 31, 1981.
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O_2. Gas samples from the flask were hand injected into the Beckman LB2 detector head and resultant concentration noted. Commercial and laboratory standards and test samples were compared at the same attenuation to avoid any changes in linearity that might occur with gain changes. Anesthetic concentrations were calculated from measurements and the line of best fit for at least seven calibration points extending over the range of applicable concentrations. Frequent calibration checks were made with one or more standards throughout each experiment.

Investigations encompassed four areas: (*a*) the effect of changes in carrier gas flow rates on delivered isoflurane concentrations at room temperature, (*b*) the effect of time on vaporizer output when carrier gas flow was kept constant, (*c*) the effect of changes in ambient temperature on vaporizer output, and (*d*) the effect of simulated intermittent positive pressure ventilation (IPPV) on vaporizer output.

Relationship of O_2 Flow Rate to Vaporizer Output

Oxygen flow rates ranged from 0.75 to 15 L/min. Isoflurane concentration was measured at a constant O_2 flow rate (0.75, 1.5, 3, 6, 9, or 15 L/min) as the vaporizer dial setting was progressively increased from 0% to 5% (i.e., 0%, 0.5%, 1%, 2%, 3%, 4%, 5%). Isoflurane concentration was measured 30 seconds after each dial change was made. After recording the delivered concentration at the highest (5%) dial setting O_2 flow through the vaporizer was stopped to permit refilling of the vaporizer and temperature equilibration. After at least 5 minutes of no O_2 flow through the vaporizer, the initial O_2 flow was then reinstituted with the dial set at 5% and the concentrations were again recorded as the dial setting was decreased at 30-second intervals. Again, after recording the delivered concentration at the last dial setting step (this time dial setting = 0%) O_2 flow through the vaporizer was stopped. Following the appropriate pause the O_2 flow was increased to the next higher flow rate and isoflurane concentrations recorded during a similar increasing then decreasing vaporizer dial setting process. After reaching the maximal O_2 flow (i.e., 15 L/min) the dial setting process was repeated as the O_2 flow rate was, in stepwise fashion, decreased to the starting flow of 0.75 L/min. Hence at least four measurements were made for each vaporizer at each dial

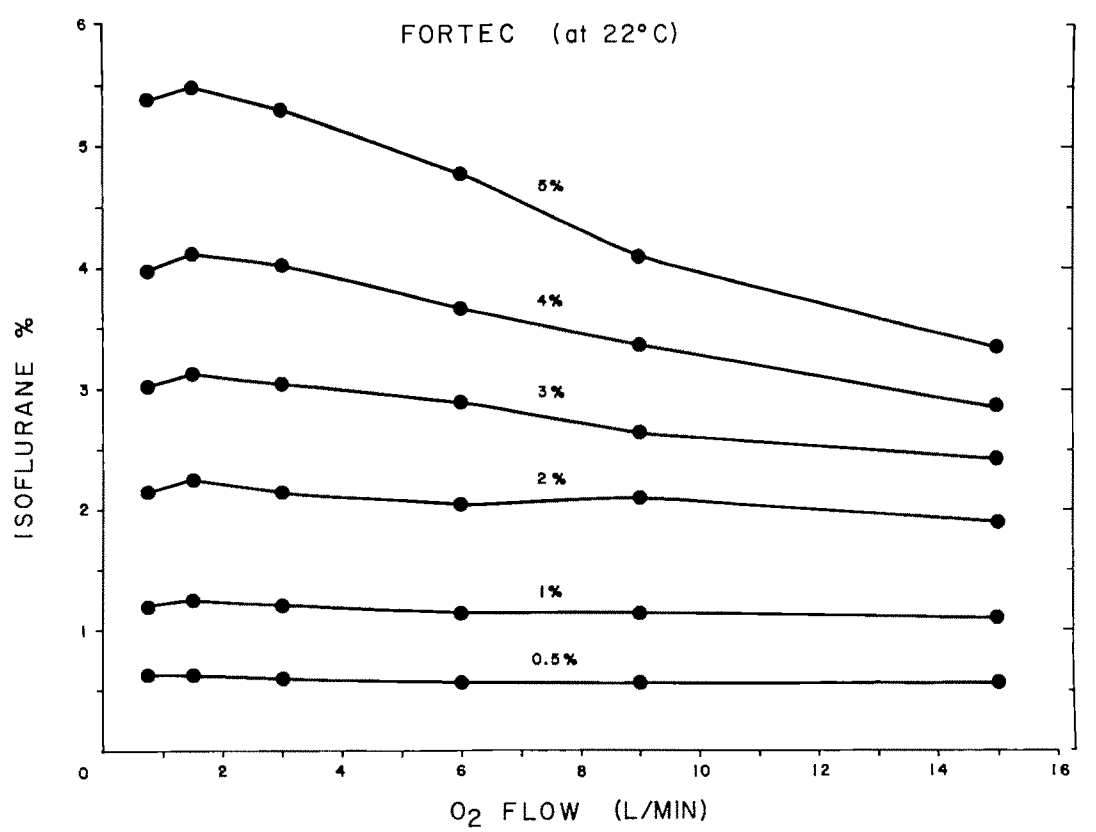


FIG 1. Percentage of isoflurane in O_2 at various flow rates and dial settings at 22°C. Figures above each curve indicate vaporizer dial settings. Data points represent average of measurements with two vaporizers.

setting-flow rate combination. The results were then expressed as the average of each combination for both vaporizers. The vaporizers were maintained at least three-fourths full with liquid isoflurane throughout the studies.

Temporal Changes in Vaporizer Output

The consistency of vaporizer output over 15 minutes of unvarying O_2 flow rate and dial setting was studied with both vaporizers. Concentrations were recorded at 0.5, 1, 2, 3, 4, 5, 10, and 15 minutes, after abruptly initiating an O_2 flow through the vaporizer at a specific vaporizer dial setting. Specific conditions included three different dial settings (1%, 3%, and 5%) at three different O_2 flow rates (3, 6, and 12 L/min). Measurements were made for 15 minutes at each concentration at 3, 6, and then 12 L/min, followed by a repeat series of similar recordings at 12, 6, and then 3 L/min. Pauses of at least 15 minutes separated each run at each dial setting. The results of the two runs for each step in both vaporizers were averaged. The vaporizer was usually refilled after each run and then gently agitated to speed mixing and temperature equilibration. At the conclusion of these studies the vaporizers were drained of liquid anesthetic and the concentration of delivered isoflurane was measured as a function of time with the vaporizer dial set at 5% and the O_2 flow rate at 12 L/min.

Relationship of Ambient Temperature to Vaporizer Output

In addition to flow-concentration and time-concentration studies at room temperature (22 ± 1°C) studies were performed with the vaporizers at 15 ± 0.5°C and 30 ± 0.5°C. Carrier gas flows of 1.5, 3, 6, and 12 L/min and vaporizer dial settings similar to earlier flow-concentration studies were used. The results of four runs at each step in each vaporizer were averaged. Temporal studies at the high and low temperatures were performed only at 5% at a 12-L/min O_2 flow rate. The results of two runs for each vaporizer were averaged.

Vaporizer temperature was altered by immersing the waterproofed vaporizers in a thermostatically controlled hot water or ice bath. Temperature, as measured by a Bureau of Standards mercury thermometer

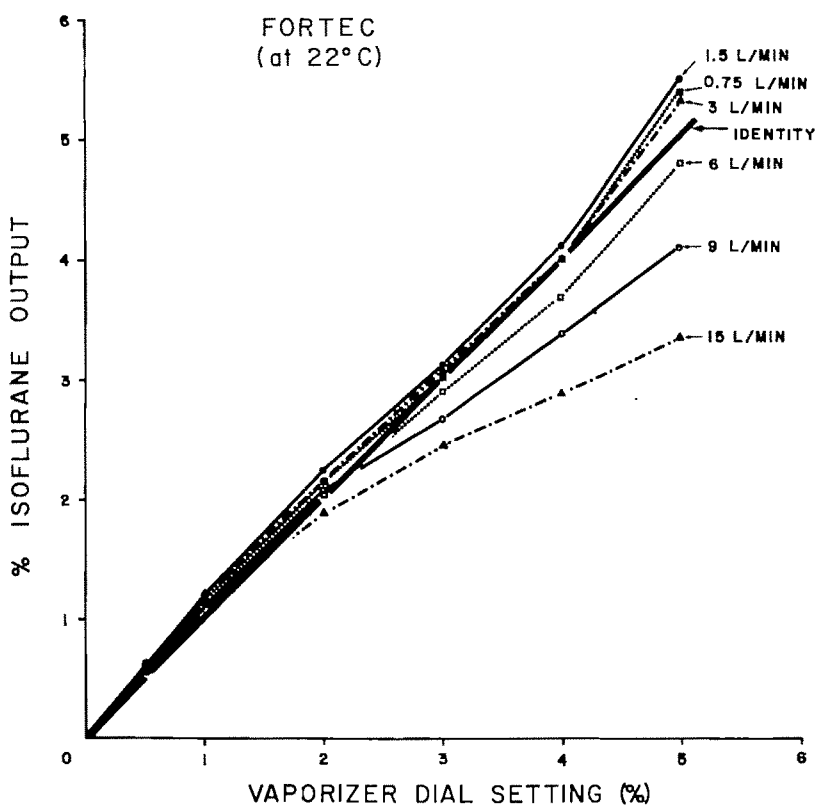


FIG 2. Percentage of isoflurane in O_2 at various vaporizer dial settings. Figures to right of each curve indicate O_2 flow rates. Data points represent average of measurements with two vaporizers.

at the midexternal surface of the vaporizer, was maintained constant for at least 30 minutes before making any concentration measurements.

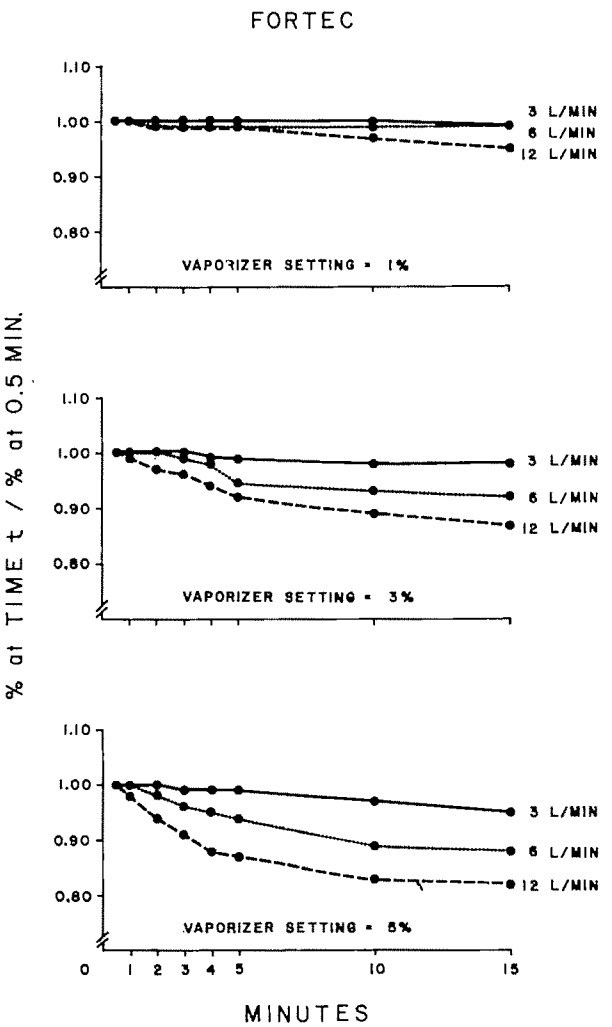


FIG 3. Temporal changes in delivered isoflurane at different dial settings and O_2 flow rates. Changes are expressed as isoflurane concentration at time of measurement and related to vaporizer output measured 0.5 minute after initiating O_2 flow at a particular dial setting. Data points represent average of measurements with two vaporizers.

Effects of Simulated IPPV

Vaporizer output was also evaluated under conditions simulating IPPV. The experimental arrangement consisted of a standard human adult circle circuit and a gas mixing/sampling apparatus attached to the vaporizer outlet via a piece of standard conductive rubber anesthetic delivery hose. A T-piece positioned just distal to the vaporizer outflow was connected to a calibrated strain gauge which permitted recording pressures downstream from the vaporizer. A low volume, rubber, artificial lung was positioned at the Y-piece of the "patient" breathing circuit and the rebreathing bag was replaced with a locally constructed "bag in box" ventilator powered by a Bird Mark IX ventilator. Measurements were made with only one of the vaporizers at vaporizer dial settings of 1%, 3%, and 5% and an O_2 flow rate of 3 L/min. At least four measurements were made at each of four different peak "inspiratory" pressures (approximately 6, 12, 25, and 48 torr) for each dial setting. The isoflurane concentration at its peak during "inspiration"/"expiration" was calculated and the resultant values were averaged. "Respiratory frequency" was 7 breaths per minute with an average "inspiratory" duration of 2 seconds.

Results

Relationship of O_2 Flow Rate to Vaporizer Output

At vaporizer dial settings of 2% or less the average delivered isoflurane concentration measured 30 seconds after a dial adjustment differed from dial settings by less than 0.25 vol% at all O_2 flow rates (Fig 1). At dial settings of 3% and greater the relationship between dial setting and delivered concentration depended largely on O_2 flow rate (Figs 1 and 2). At low O_2 flow rates delivered concentrations were usually greater than dialed settings and at higher O_2 flows delivered concentrations were less than anticipated from the dial position. A maximal divergence of 1.65 vol% was found at a dial setting of 5% and an O_2 flow

TABLE 1

Isoflurane Concentration and Volume Change following 15 Minutes of Use at 22°C and Indicated Conditions*

	O_2 Flow (L/min)/vaporizer setting (%)								
	3/1	6/1	12/1	3/3	6/3	12/3	3/5	6/5	12/5
Change in delivered isoflurane (vol%)	0.02	0.02	0.06	0.08	0.26	0.37	0.31	0.63	0.78
Change in vaporizer liquid isoflurane volume (ml)	4.0	6.0	11.5	7.7	13.8	25.5	12.5	23.0	36.3

* Average of measurements from studies with two vaporizers.

of 15 L/min. Vaporizer output most closely approximated dial setting at approximately 4 L/min for all dialed isoflurane concentrations (Fig 1). Multiple measurements for a given vaporizer under similar conditions usually varied by no more than 10%.

Temporal Changes in Vaporizer Output

Time-related changes in delivered isoflurane concentration for a given constant O_2 flow rate and vaporizer dial setting are given in Fig 3 and Table 1. In general, as O_2 flow rate or vaporizer dial setting (or both) increased vaporizer output decreased with time. Little change occurred in isoflurane delivery at O_2 flows of 6 L/min or less and low vaporizer settings. Conversely, significant reductions in isoflurane delivery occurred with time at high flow rates and maximal dial settings. Maximal reductions in delivered isoflurane over 15 minutes occurred at a vaporizer setting of 5% and an O_2 flow rate of 12 L/min. The average temporal decay of isoflurane for the two vaporizers emptied of liquid anesthetic is shown in Fig 4. Trace quantities of isoflurane were still detectable at 20 minutes when measurements were halted.

Relationship of Ambient Temperature to Vaporizer Output

Increasing (to 30°C) or decreasing (to 15°C) the temperature of the environment immediately surrounding the vaporizer altered the output when compared with conditions at 22°C (Figs 5 and 6). Although temperature-related changes were minimal at the 1% dial setting for all carrier gas flow rates, marked changes occurred at the 3% and especially the 5% settings. For both vaporizer settings the changes in delivered concentration noted with O_2 flow rates at room temperature were paralleled by results at both high and low temperature conditions. However, for a given condition absolute isoflurane concentration was lowest with the low temperature and greatest with the high environmental temperature. The magnitude of change was most pronounced at 30°C. Temporal reductions in delivered isoflurane were most evident

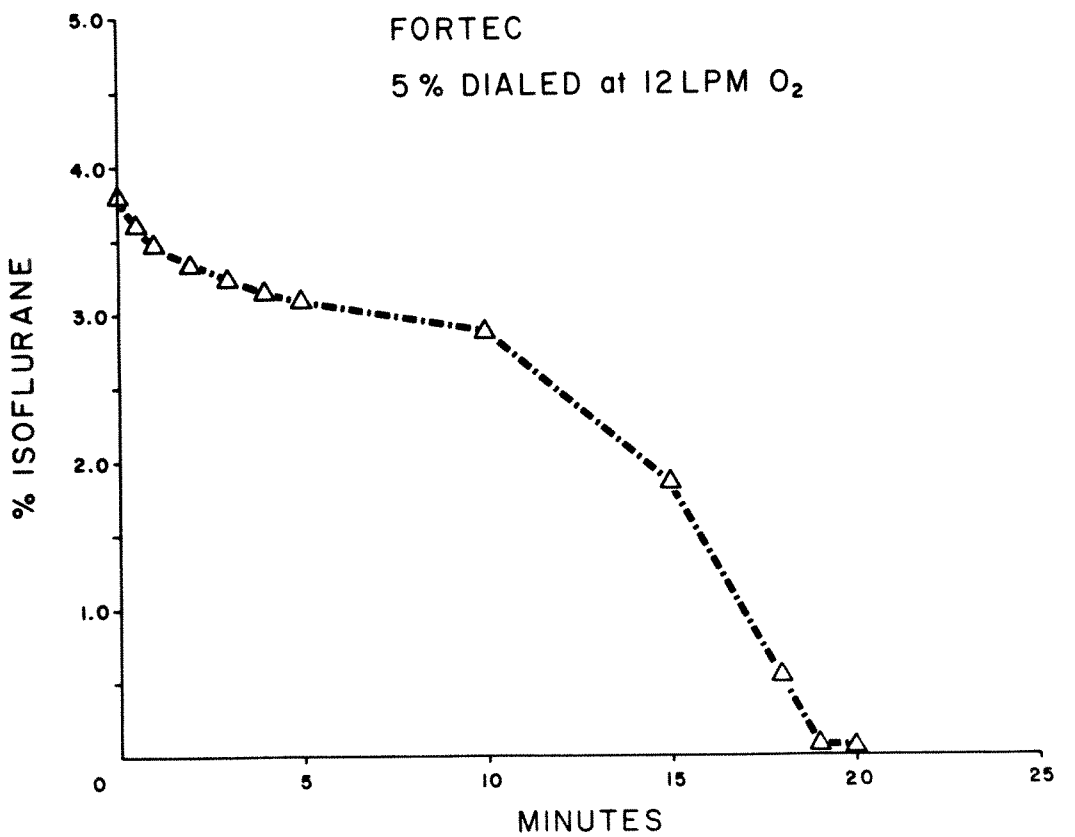


FIG 4. Temporal decay of delivered isoflurane following drainage of liquid anesthetic from vaporizer. Changes are expressed as isoflurane concentration at time of measurement relative to vaporizer output measured 0.5 minute after initiating O_2 flow. Data points represent average of measurements with two vaporizers.

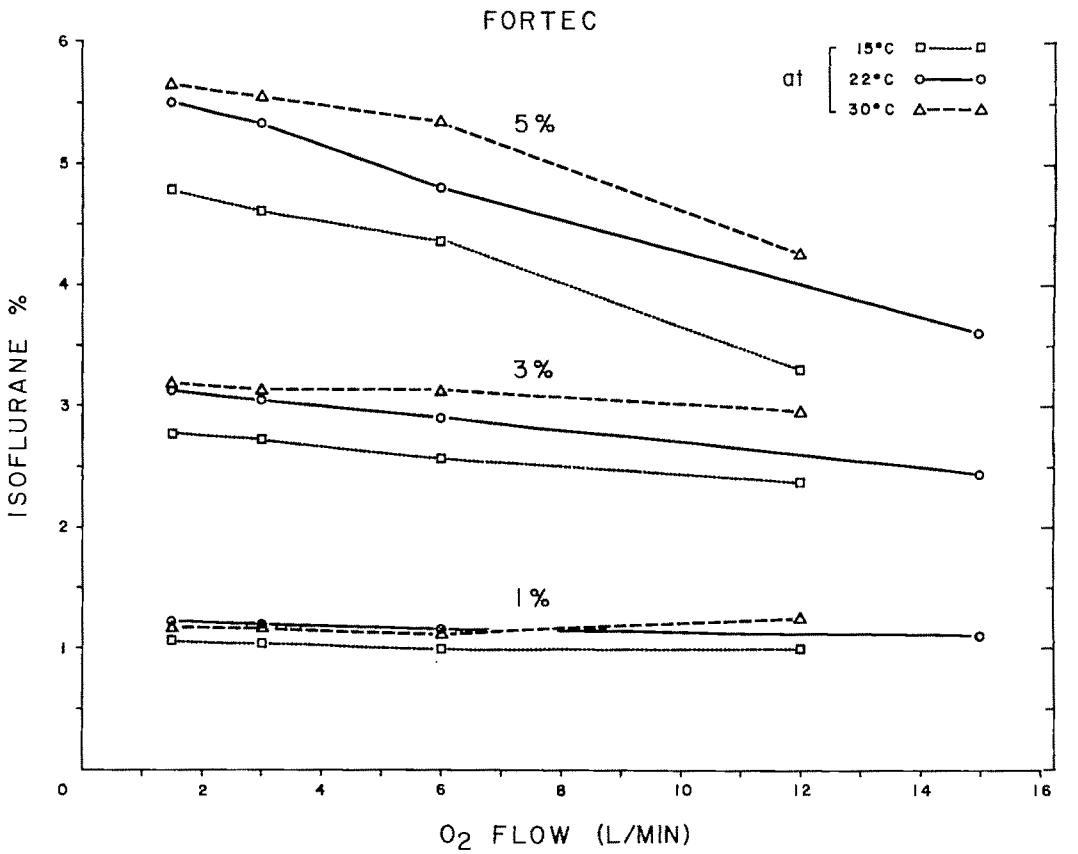


FIG 5. Percentage of isoflurane in O_2 at various dial settings and O_2 flow rates at environmental temperatures 15, 22, and 30°C. Dial settings are indicated above each group of curves. Data point represent average of measurements with two vaporizers.

during conditions of 5% dialed and 12 L/min O_2 flow rate for all temperatures studied. However, reductions were least at 15°C (Fig 6).

Effects of Conditions Simulating IPPV

Little to no effect on vaporizer output was noted with IPPV simulation up to breathing circuit pressures of 25 torr (Table 2). At peak inspiratory pressures averaging 48 torr, delivered inspiratory isoflurane concentrations increased slightly.

Discussion

The intent of this study was to evaluate the performance of the new Fortec vaporizer during a number of real and simulated operational conditions. Results from the two vaporizers studied indicate that the Fortec vaporizer is as efficient in delivering isoflurane as a previous study has shown the Fluotec (a Cyprane precision vaporizer for halothane) to be in its delivery of halothane under similar conditions (2).

At 4 L/min the vaporizer output was nearly identical with the dial setting (Fig 1). However, at 12 L/min the output initially averaged approximately 3.75% when the vaporizer dial was set at 5% (and even less at 15 L/min to approximately 3.35%). After 5 minutes at these vaporizer/O_2 flow settings there is a further decrease of close to 15% reducing the actual vaporizer output to approximately 3.2%; at 15 minutes the vaporizer output is approximately 3.0% isoflurane (Fig 3). The temporal reduction in delivered isoflurane concentration at high O_2 flow rates and vaporizer dial settings that we found is in qualitative agreement with the results of the halothane-Fluotec studies of Paterson et al. (2). Changes with time are presumably related to the rapid vaporization of the anesthetic and the accompanying progressive reduction in liquid anesthetic temperature and saturated vapor concentration. Because of these marked temporal changes, especially at high anesthetic carrier gas flow rates, it is imperative that sampling times be precisely defined when vaporizer dial settings are compared with actual

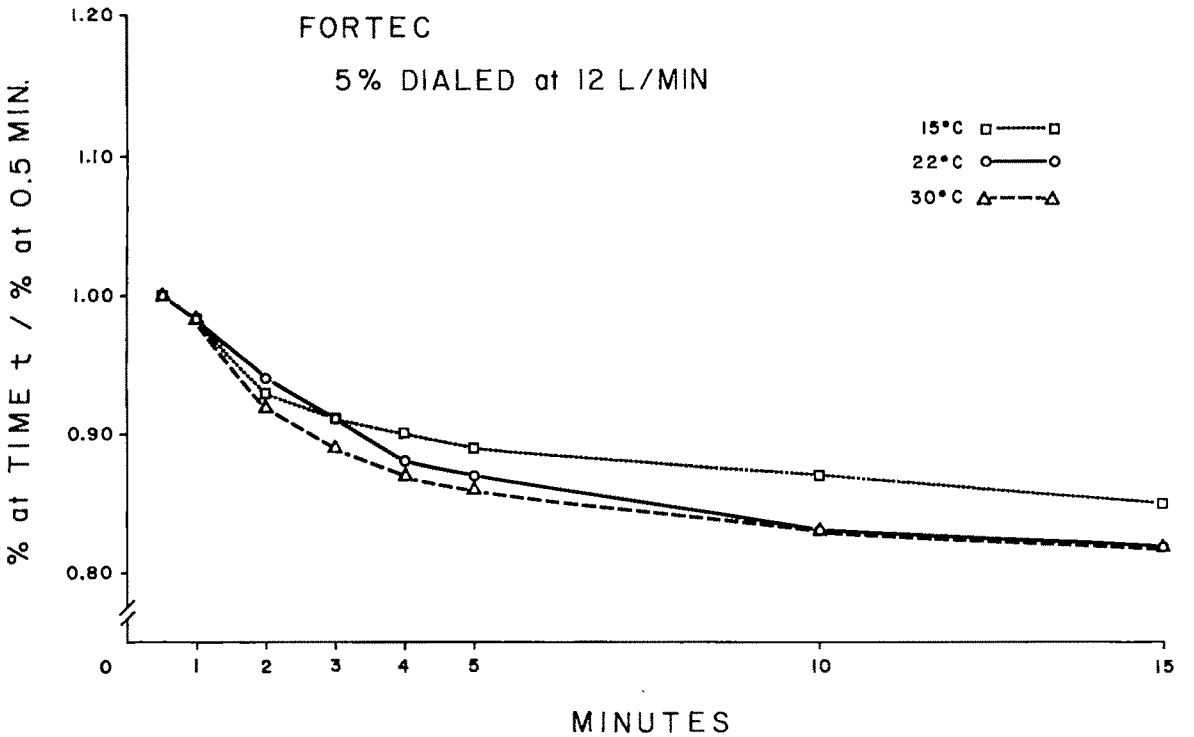


FIG 6. Temporal reductions in delivered isoflurane at environmental temperatures of 15, 22, and 30°C. Changes are expressed as isoflurane concentration at time of measurement relative to vaporizer output measured 0.5 minutes after initiating O_2 flow. Data points represent average of measurements with two vaporizers.

TABLE 2

Effect of Intermittent Positive Pressure on Output of Fortec at 22°C

Vaporizer setting	Av peak inspiratory pressure	Av change in isoflurane concentration, inspiration/expiration
	torr	
1	5.7	1.00
	12.5	1.01
	25.0	1.05
	48.1	1.17
3	5.7	1.00
	12.5	1.01
	25.0	1.04
	48.1	1.11
5	5.7	1.00
	12.5	1.01
	25.0	1.03
	48.1	1.16

anesthetic concentrations. These results further emphasize the significant limitations inherent in using vaporizer dial settings as a precise measure of anesthetic dose in experimental preparations, particularly in the presence of elevated gas flow rates and/or extremes in environmental temperature.

In our studies we used 100% O_2 as the carrier gas. However, in the clinical setting nitrous oxide (N_2O) is frequently added to the gas entering the vaporizer. Readers should be aware that under these circumstances delivered isoflurane may not be exactly comparable to conditions reported here. Although we did not determine the influence of N_2O on vaporizer output of isoflurane, previous studies have indicated that carrier gas mixtures of O_2/N_2O increase the output of Cyprane Mark II halothane (Fluotec) vaporizer (3, 4), reduce the output of the Ohio enflurane vaporizer (5, 6), and either reduce or have little or no effect on the performance of the Cyprane Mark III halothane and Cyprane enflurane vaporizer (2, 6, 7).

ACKNOWLEDGMENTS

Isoflurane was supplied by Pitman Moore Inc., Washington Crossing, NJ. Vaporizers were supplied by Pitman Moore Inc. and Fraser Harlake Inc., Orchard Park, NY.

REFERENCES

1. Sawyer DC, Eger EI II, Bahlman SH, Cullen BF, Impelman D. Concentration dependence of hepatic halothane metabolism. Anesthesiology 1971;34:230–5.
2. Paterson GM, Hulands GH, Nunn JF. Evaluation of a new halothane vaporizer: the Cyprane Fluotec Mark 3. Br J Anaesth

1969;41:109–19.
3. Stoelting RK. The effect of nitrous oxide or halothane output from Fluotec Mark 2 vaporizer. Anesthesiology 1971;35:215–8.
4. Diaz PM. The influence of carrier gas on the output of automatic plenum vaporizers. Br J Anaesth 1976;48:387–91.
5. Stoelting RK, Nawaf K. Enflurane vaporizer accuracy with nitrous oxide (letter). Anesth Analg 1979;58:441.
6. Prins L, Strupat J, Clement J, et al. An evaluation of gas density dependence of anaesthetic vaporizers. Can Anaesth Soc J 1980;27:106–10.
7. Lin CY. Assessment of vaporizer performance in low-flow and closed-circuit anesthesia. Anesth Analg 1980;59:359–66.

Intraoperative Anticoagulation in Cardiovascular Surgery

The kinetics of heparin effect was studied in 28 patients undergoing peripheral vascular and cardiac operations. The activated clotting time (ACT) was measured in seconds by an electronic clot timer. The maximum ACT after initial heparin administration, the time to reach maximum ACT, and the half-time of heparin effect (t½) were determined. The anticoagulant effect of a given dose of heparin varied greatly among the patients. No correlation was found between the t½ and the dosage of heparin administered. Despite higher doses of heparin administered to cardiac patients, the t½ in cardiac and vascular patients was not significantly different. Four patients received the same dose of heparin preoperatively and intraoperatively in an effort to predict the intraoperative effect. The times to maximum effect were the same but t½ intraoperatively was longer. These results indicate: (1) maximum heparin effect occurs later than previously believed and is different for cardiac and peripheral vascular patients; (2) the recommendation to give more heparin based on the 5-minute ACT is not valid; (3) individual response to a standard dose of heparin is unpredictable, both in duration and maximum effect; and (4) intraoperative monitoring of the heparin effect is practical and is the only way that any consistent, specific end point of heparin can be achieved. (*Effeney DJ, Goldstone J, Chin D, Krupski WC, Ellis RJ. Intraoperative anticoagulation in cardiovascular surgery. Surgery 1981;90:1068–74*)

CLINICAL reports

Differential Diagnosis of Hand Ischemia in the Presence of an Arterial Cannula

Jeffery S. Vender, MD,* and David R. Watts, MD, FACS†

Utilization of indwelling arterial catheters for continuous blood pressure monitoring and blood sampling has become an accepted standard of practice in appropriate situations. Symptomatic arterial occlusion as a consequence of radial artery cannulas has been previously reported (1). The following case report is an example of arterial occlusion initially attributed to a radial artery cannula, but eventually felt to be secondary to arterial embolization from a proximal source.

Case Report

A 41-year-old white man was admitted to the hospital in February 1981 for evaluation of lingular atelectasis. He had previously been hospitalized for episodes of pneumonia, pleural effusions, hemoptysis, and bronchiectasis. Previous pulmonary evaluations were negative for malignancy. A bronchogram demonstrated complete lingular obstruction. A left thoracotomy and sequential resection were planned.

Past history included a myocardial infarction in 1972 and left carotid endarterectomy in 1974. In 1976, a right brachial artery cardiac catheterization demonstrated "limited coronary artery disease and non-surgical therapy [was] recommended." There was no history of previous anesthetic problems. Present medications included hydrochlorothiazide, oral propranolol, 40 mg three times per day, and isosorbide dinitrate. There were no known allergies. The patient had smoked two packs of cigarettes per day until 1972.

Preoperative examination revealed decreased breath sounds in the left anterior lung field; no gallops, murmurs, or bruits were detected. Arterial pulses were 2+ and equal bilaterally. Allen's test of both hands showed patent palmar anastomoses between radial and ulnar arteries with return of hand color in less than 5 seconds. Significant laboratory data included: hemoglobin, 17 g/dl; serum cholesterol level, 293 mg/dl (normal <250 mg/dl); and total serum bilirubin level, 1.6 mg/dl (normal 0.1 to 1.0 mg/dl). Preoperative pulmonary functions were interpreted as indicative of mild-to-moderate obstructive/restrictive disease. Electrocardiogram showed an old anterior wall myocardial infarction and a gated cardiac blood pool examination showed decreased left ventricular wall motion in the septal region and paradoxical wall motion involving the anterior basal and lateral basal segments of the left ventricle. The ejection fraction was 57%.

Before the induction of anesthesia, a 16-gauge peripheral intravenous catheter was inserted. After an unsuccessful attempt at a left radial artery cannulation, a 20-gauge, 2-inch (Deseret Angiocath) indwelling catheter was placed atraumatically on the first attempt in the right radial artery. A continuous infusion of heparinized 0.9% normal saline (2 units of heparin/ml) was maintained at a rate of 3 ml/hr with an Intraflow system (Gould, Oxnard, CA). After insertion of the radial catheter, the right hand was warm with good capillary refill in the nail beds. The catheter was connected to a Saturn monitor, permitting beat-by-beat oscilloscope display of the pulse contour and transduced blood pressure.

With other appropriate monitors in place, anesthesia was induced. Vital signs remained stable after induction and during and after tracheal intubation. After bronchoscopy, the patient was placed in the right lateral position, a pad inserted in the axilla, and the right arm positioned to prevent stretch on the brachial plexus. After positioning, there were no changes in vital signs and the appearance of the right

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Received from the Department of Surgery, Division of Anesthesia, Evanston Hospital, Evanston, Illinois; Northwestern University Medical School, Chicago, Illinois. Accepted for publication December 28, 1981.

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hand remained unchanged. Surgery proceeded without incident. The transduced radial arterial pressure tracing was continuously observed without variation in the quality of the oscilloscopic tracing. The right hand was visualized throughout the operative procedure (remaining pink and warm). Estimated blood loss was 600 ml; 2700 ml of crystalloid solution was given. The patient was taken to the recovery room, extubated and awake, where blood pressure was 130/70, heart rate was 76 beats per minute and regular, and respiratory rate was 20 breaths per minute, with no subjective complaints. The transduced radial pressure was monitored continuously, and the radial cannula functioned without problems.

Approximately 12 hours after surgery, the patient complained of numbness and tingling in the right hand. The arterial cannula was removed immediately but without subjective improvement. Initial evaluation showed a "cool" right hand, no palpable radial, ulnar, or brachial pulses, and

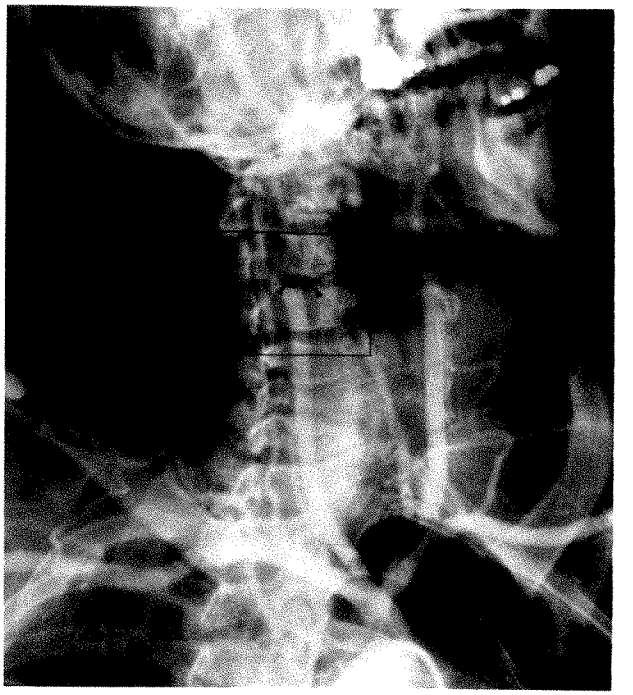


FIG 1. Thoracic arch aortogram with catheter in ascending aorta demonstrating saddle embolus (arrows) at right common carotid bifurcation. A 4-cm clot can be seen extending up proximal portion of right internal carotid artery; smaller 1.5-cm slot can be seen within proximal right external carotid artery.

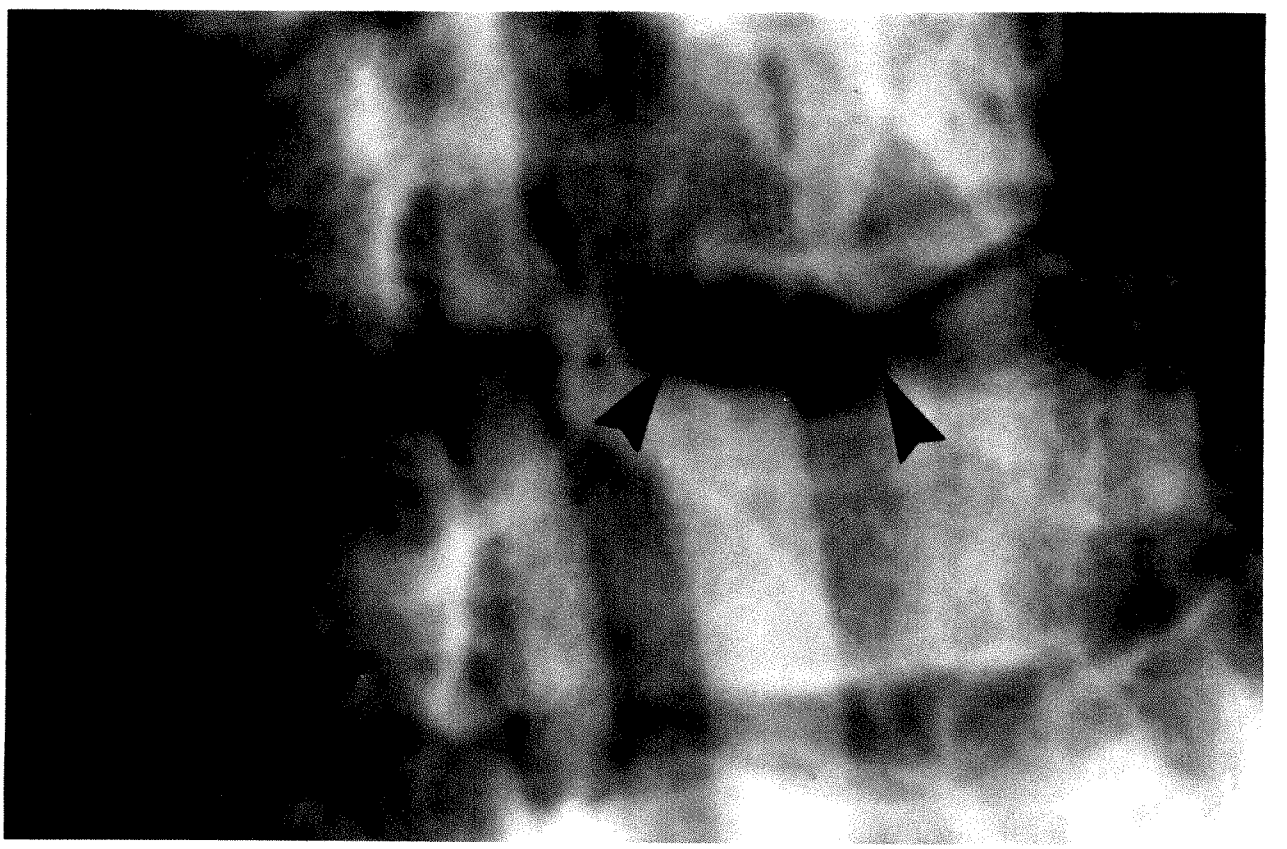


FIG 2. Magnification of area shown in box in Fig 1.

a weakly palpable axillary pulse. Doppler studies revealed a brachial flow signal. The nailbeds on the right hand were dusky with poor capillary refill. Muscle strength of the right hand was assessed as normal. A vascular surgeon advised that the hand be placed in a dependent position, wrapped in blankets, and that papaverine and low molecular weight dextran be given. Two hours after initiation of therapy, numbness and tingling was less but the hand remained cool. The consulting vascular surgeon felt that a proximal arterial obstruction existed. An arteriogram was ordered for further evaluation. Before the procedure was performed (approximately 8 hours after decannulation), the patient developed neurologic symptoms characterized by a left facial droop and complete left hemiparesis.

An arch aortogram showed a "saddle embolus" at the right common carotid bifurcation extending into the proximal portions of the right external and internal carotid (Figs 1 and 2). In addition, occlusion of the right axillary artery, approximately 3 cm lateral to the margin of the right scapula, was noted (Fig 3). The patient underwent a right axillary and brachial embolectomy under local anesthesia. Postoperative angiogram showed complete perfusion of the right upper extremity. Inspection of the brachial artery showed no stenosis in the area of the previous cardiac catheterization. Aftery surgery the patient's symptoms in the right hand were completely resolved. Carotid embolectomy was considered but was felt inadvisable. Final consultative evaluations determined that the events which transpired in this patient were probably due to embolization from a left ventricular aneurysm.

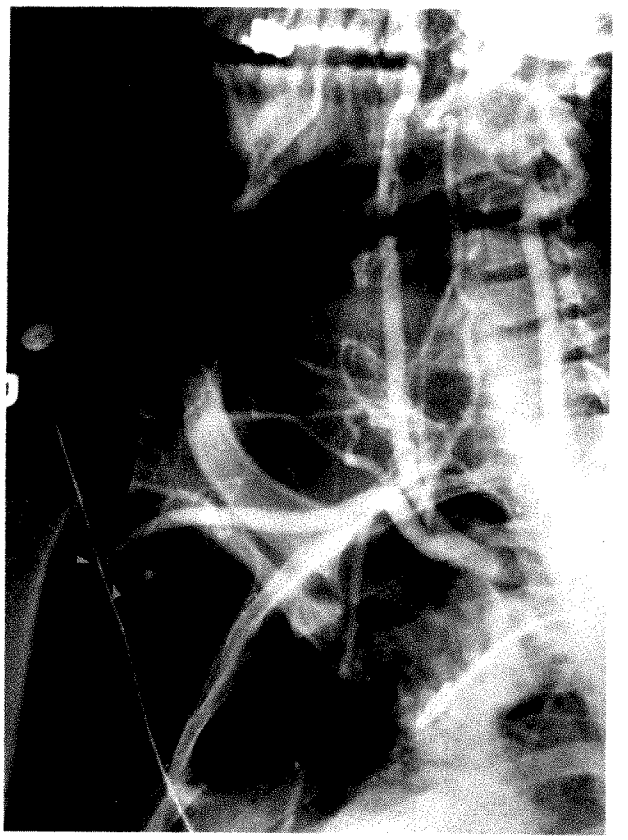


FIG 3. As right axillary artery crosses margin of lateral border of scapula there is occlusion of right axillary artery (arrowheads).

Discussion

Acute arterial vascular complications of the hand are not limited to radial artery cannulation (1). Systemic embolization from a cardiac source has been previously described as causing upper extremity ischemia (2). A recent study (3) revealed a high association of left ventricular thrombi and left ventricular aneurysms. The incidence of embolization associated with left ventricular mural thrombi has been reported as 5%. Other series have shown a 0 to 52% incidence of systemic embolization associated with left ventricular mural thrombi, the incidence varying with the method of detection. With autopsy confirmation, the reported incidence is 30% and surgical confirmation 6%.

Thrombosis as a consequence of percutaneous radial artery cannulation has been reported numerous times in the literature. Despite the high reported incidence of thrombus formation, the majority of radial artery thrombi following cannulation are asymptomatic and the frequency of severe vascular sequela minimal (4, 5). Multiple factors have been implicated in thrombus formation, including duration of cannulation, traumatic insertion, catheter size, catheter configuration, catheter material, presence of an abnormal Allen's test, hypercoagulable states, decreased perfusion, size of precannulated artery, and post-decannulation compression (1, 6). Thrombi can also develop following removal of a radial arterial cannula (5), and cases of retrograde arterial embolization have been reported (7). Retrograde embolization is thought to occur from unrestricted flushing of arterial cannulas or arterial-venous shunts (e.g., Scribner shunt) (7, 8).

This case report emphasizes the need for complete evaluation of patients with arterial occlusion following radial arterial cannulation. Although arterial cannulas may cause hand ischemia, they are not the only etiology. Only with thorough diagnostic efforts can appropriate therapeutic decisions be made.

REFERENCES

1. Baker RJ, Chunprapaph B, Nyhus LM. Severe ischemia of the hand following radial artery catheterization. Surgery 1976;80:449-51.

2. Samaan H. The hazards of radial artery pressure monitoring. J Cardiovasc Surg 1971;12:342–7.
3. Reeder GS, Lengyel M, Tajik AJ, et al. Mural thrombus in left ventricular aneurysm. Mayo Clin Proc 1981;56:77–81.
4. Downs JB, Rackstein AD, Klein EF, Hawkins IF. Hazards of radial artery catheterization. Anesthesiology 1973;38:283–6.
5. Bedford RF, Wollman H. Complication of percutaneous radial artery cannulation. Anesthesiology 1973;38:228–36.
6. Kim JM, Arakawa K, Bliss J. Arterial cannulation: factors in the development of occlusion. Anesth Analg 1975;54:836–41.
7. Gann E, Mallick NP, Brewis RAL, et al. Cerebral damage from declotting Scribner shunts. Lancet 1969;2:77–9.
8. Lowenstein E, Little JW, Lo HH. Prevention of cerebral embolization from flushing radial artery cannulas. N Engl J Med 1971;285:1414–6.

Vasodilator Therapy after Myocardial Infarction

Hemodynamic changes and mortality and morbidity were compared in a randomized controlled trial of sodium nitroprusside after acute myocardial infarction. Fifty patients with a mean pulmonary capillary wedge pressure of more than 20 mm Hg within 24 hours of acute infarction were randomly assigned to one of two groups: 25 patients were treated with nitroprusside and 25 with furosemide. Nitroprusside rapidly produced a sustained decrease in systemic vascular resistance and increase in cardiac index (thermodilution). After 1 hour the cardiac index had increased 16 ± 3% (mean ± SE) ($p < 0.001$) compared with a decrease of 7 ± 3% with administration of furosemide ($p < 0.01$). Differences in systemic vascular resistance and cardiac index in the two groups persisted throughout the 48-hour treatment period ($p < 0.001$). Pulmonary capillary wedge pressure decreased rapidly with nitroprusside and slowly with furosemide so that, although it was significantly lower in the former group overall ($p < 0.001$), by 48 hours the values were not different. Although beneficial acute hemodynamic effects of nitroprusside were demonstrated, there was no difference in mortality or in morbidity assessed clinically, by chest x-ray, echocardiogram, or graded treadmill stress testing after 6 months or 1 year. (*Hockings BEF, Cope GD, Clarke GM, Taylor RR. Randomized controlled trial of vasodilator therapy after myocardial infarction. Am J Cardiol 1981;48:345–52*)

ANESTH ANALG
1982;61:469-70

Treatment of Traumatic Tooth Avulsion

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Teeth are held to the alveolar bone by collagenous tissue known as Sharpey's fibers, which form the periodontal ligament. When a tooth is avulsed, these fibers are severed with some remnants of the ligament remaining attached to the bone and some to the tooth. Replantation, if feasible, preserves function and aesthetic appearance and militates against additional dental procedures such as replacement by fixed or removable prostheses.

The maxillary incisor teeth are at more risk of traumatic injury than other teeth. Numerous reports in the dental and anesthesia literature (1–4) acknowledge the vulnerability of the maxillary incisors during tracheal intubation. The objective of this paper is to present a sequence of emergency treatment for teeth inadvertently avulsed during anesthesia, or surgery, or both.

Procedure

What should the anesthesiologist do when confronted with an avulsed tooth? First, the anesthesiologist should evaluate the tooth. For successful replantation, the tooth should be without extensive decay, fracture, or evidence of advanced periodontal disease. If the periodontal status is unclear, it can be estimated by inspecting the teeth that were adjacent to the avulsed tooth. Also, the alveolar socket should be examined for major fracture or comminutions. Any blood clot within the alveolus should be removed by irrigation and not by curettage.

Damage to or removal of the periodontal ligament during replantation results in osseous replacement or inflammatory root resorption (5, 6); retention of the periodontal ligament on the root and bone surfaces promotes replantation. Therefore, it is imperative not to damage the ligamental fibers that remain attached to the avulsed tooth or to the alveolar socket. Therefore, curettage of the tooth or the socket should not be performed and disinfectants should not be used. The root should be handled minimally, and, if it is necessary to remove debris, the tooth should be rinsed with normal saline or gently cleansed by using saline-moistened gauze. The root should not be allowed to dry; if the tooth cannot be immediately replanted, it must be wrapped in a piece of gauze moistened with saline.

There is general agreement that the less time the tooth is out of its socket, the more successful the replantation will be as this time period directly relates to the vitality of the periodontal ligament. A 90% success rate occurs if the extraoral period does not exceed 30 minutes. In contrast, after 2 hours, successful replantation is likely only approximately 5% of the time (7–9).

For replantation, the avulsed tooth should be reinserted into the socket slowly to allow fluids at the base of the socket to escape. If the tooth is forced abruptly into the socket, the pressure of the trapped fluid will extrude the tooth. If it extrudes even after slow, gentle replantation, 10 to 15 minutes of continuous pressure will usually enable satisfactory replantation.

A reimplanted tooth requires stabilization to keep the tooth in its original position within the bone. It is important that the stabilization technique be passive, not active. Dental consultation should be obtained as soon as possible because a stabilization splint may be required for several weeks. However, in the interim, some simple mode of stabilization should be provided immediately after replantation. One possible method is the cross-suture splint (10). This technique uses a figure-eight suture which starts at the buccal gingiva, extends over the incisal edge of the tooth, is passed into the palatal gingiva, and finally is returned over the tooth and tied at the starting point. Although this technique has limitations, it serves well as a temporary splint.

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Discussion

Upon replantation, healing of the traumatized tissue follows one of three courses. (a) Normal function of the periodontal ligament is restored. Microscopically, areas of superficial resorption are filled by new cementum, i.e., the outer layer of cells on the root of the tooth. There is minor damage to the periodontal ligament, but no lasting deleterious effect on the tooth. (b) With fusion or ankylosis of the root to bone, organization of a blood clot in the periodontal ligament causes the formation of granulation tissue and eventual replacement by bone (6). The root of the ankylosed tooth potentially can undergo osseous replacement. This ossification eventually may cause the loss of the tooth. (c) If inflammation communicates with a necrosed tooth pulp, root resorption is intensified and the periodontal ligament fails to heal. An ideal tooth replantation would be characterized by little surface resorption and no osseous replacement or root resorption.

REFERENCES

1. Andreasen JO. Traumatic injuries of the teeth. St Louis: CV Mosby Co, 1972:141–227.
2. Blanc VF, Tremblay NAG. The complications of tracheal intubation: a new classification with a review of the literature. Anesth Analg 1974;53:202–13.
3. Wright RB, Manfield FFV. Damage to teeth during the administration of general anesthesia. Anesth Analg 1974;53:405–8.
4. Orringer MB. Endotracheal intubation and tracheostomy: indications, techniques, and complications. Surg Clin North Am 1980;60:1447–64.
5. Andreasen JO. The effect of splinting upon periodontal healing after replantation of permanent incisors in monkeys. Acta Odontol Scand 1975;33:313–23.
6. Hammer H. Replantation and implantation of teeth. Int Dent J 1975;5:439–57.
7. Andreasen JO. Treatment of fractured and avulsed teeth. J Dent Child 1971;38:29–31, 45–8.
8. Massler M. Tooth replantation. Dent Clin North Am 1974;18:445–52.
9. Scott JN, Zelikow R. Replantation—a clinical philosophy. J Am Dent Assoc 1980;101:17–9.
10. Neaverth EJ, Georig AC. Technique and rationale for splinting. J Am Dent Assoc 1980;100:56–63.

ANESTH ANALG
1982;61:471-2

Superficial Cervical Plexus Damage as a Result of a Back Roll

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It is customary at our institution to place a rolled sheet between the scapulae of patients having cardiac surgery through a median sternotomy. This facilitates sternal incision and retraction, but invariably places the neck in a hyperextended position. Although we have not previously had any problems associated with this practice, the occurrence of nerve damage due to overextension (1, 2) and compression (3, 4) of nerves under anesthesia has been well documented (5). The purpose of this report is to bring attention to the potential cervical plexus damage that can occur from intrascapular rolls.

Case Report

The patient was a 54-year-old white man with a history of rheumatic heart disease and three myocardial infarctions. Preoperative medications included propranolol, 20 mg four times a day; digoxin, 0.25 mg daily; papaverine, 1 mg twice a day; and nitroglycerine as needed. Due to increasing exertional angina the patient entered our institution for corrective cardiac surgery. Pertinent physical findings included blood pressure of 120/70 torr, supple neck without masses, and midline trachea. Roentgenogram showed no evidence of cervical arthritis nor presence of a cervical rib. Vessels in the left side of the neck were not used for monitoring lines. The patient had a fentanyl-oxygen-pancuronium anesthetic with an intravenous infusion of nitroglycerin. Following tracheal intubation a rolled sheet was placed between the scapulae.

Mean systemic arterial pressure never decreased below 55 torr and the lowest nasopharyngeal temperature was 21°C. During an uneventful 5-hour procedure the mitral valve was replaced and three coronary artery bypass grafts were performed.

On the following day the patient noted "tingling" of the skin overlying his left ear. Neurologic evaluation revealed an area of numbness to pinprick and light touch in an upside-down, tear drop-shaped area that encompassed the left ear including the adjacent occipital and submandibular skin and extended down the neck. There was no loss of hearing or motor function. The diagnosis of left-sided superior superficial cervical plexus injury was made and the damage was felt to be transient in nature. However, at discharge 14 days later the extent and degree of hypesthesia persisted and were unchanged at the 4-month follow-up visit.

Discussion

Various peripheral neuropathies have been reported following cardiovascular surgery. Some of these injuries can be directly related to abnormal compression or stretch on the nerves, as in the positioning of the arms (2) or in over-retraction of the median sternal incision (6). However, other factors that have been associated with such damage include hypothermia (7, 8), hypotension, and duration of surgery (9). These factors can aggravate primary nerve tissue destruction produced by stretch or compression. As hypothermia and relative hypotension are normally encountered during cardiopulmonary bypass surgery and as cardiac surgical procedures tend to be lengthy, patients undergoing such operations are at increased risk for developing nerve damage.

In our patient the distribution of sensory loss corresponded to the area innervated by C2-3 cervical nerve roots in the lesser occipital and greater auricular nerves. Injury could have been produced by hyperextension of the neck with resultant damage to: (*a*) both of the peripheral nerves, (*b*) C2-3 nerve roots, or (*c*) a portion of the superficial cervical plexus. It is possible that both the peripheral nerves were injured, but this would have required insult to two anatomic sites. Also, it is doubtful that the site of injury was the cervical roots as motor fibers are more sensitive to injury than sensory fibers (2) and no loss of motor function was noted. Therefore, the damage most likely occurred in the superior portion of the superficial cervical plexus. On cervical hyperextension either the plexus could have been compressed between the vertebral bodies and the sternocleidomas-

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Received from the Departments of Anesthesiology, Deborah Heart and Lung Center, Browns Mills, New Jersey, and University of Pennsylvania, Philadelphia, Pennsylvania. Accepted for publication January 19, 1982.

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toid muscle or the plexus could have been directly stretched (10).

The only other report of nerve damage secondary to back roll concerned damage to the circumflex nerve of the arm from a towel placed behind the shoulders (11). At present we are using intrascapular rolls only upon specific request by the surgeon. If such a roll is used, the neck is placed in a neutral position by elevating the occiput with a folded sheet.

REFERENCES

1. Clausen EG. Postoperative ("anesthetic") paralysis of the brachial plexus. Surgery 1942;12:933–42.
2. Jackson L, Keats AS. Mechanism of brachial plexus palsy following anesthesia. Anesthesiology 1965;26:190–4.
3. Garland H, Moorehouse D. Compressive lesions of the external popliteal (common peroneal) nerve. Br Med J 1952;2:1371–8.
4. James F. Hypesthesia of the tongue. Anesthesiology 1975;42:359.
5. Lincoln J, Sawyer H. Complications related to body positions during surgical procedures. Anesthesiology 1961;22:800–9.
6. Kirsh M, Magee K, Gango O, et al. Bracheal plexus injury following median sternotomy incision. Ann Thor Surg 1971;11:315–9.
7. Stephens JW. Neurological sequelae of congenital heart surgery. Arch Neurol 1962;7:450–8.
8. Swan H, Virtue R, Blount G, et al. Hypothermia in surgery. Ann Surg 1955;142:382–400.
9. Britt BA, Gordon RA. Peripheral nerve injuries associated with anaesthesia. Can Anaesth Soc J 1964;11:514–36.
10. Gray H, Goss CM. Anatomy of the human body. Philadelphia: Lea & Febinger, 1973:954–60.
11. Ellul JM, Notermans SLH. Paralysis of the circumflex nerve following general anesthesia for laparoscopy. Anesthesiology 1974;41:520–1.

Terbutaline and Maternal Cardiac Function

The effect of terbutaline sulfate on left ventricular size and performance was studied by M-mode echocardiography in 16 healthy pregnant women with premature labor. Patients with uterine activity initiated during either oxytocin challenge testing or induction of labor served as a comparison group. During terbutaline therapy, heart rate, ejection fraction, and cardiac output increased significantly. End-diastolic volume and systolic blood pressure were unchanged, and diastolic blood pressure and end-systolic volume fell. No changes in echocardiographic or hemodynamic parameters were present during oxytocin-induced uterine activity. Terbutaline, as currently used to prevent premature labor, is a potent inotropic and chronotropic agent. Pulmonary edema accompanying terbutaline treatment is probably not due to cardiac failure. (*Wagner JM, Morton MJ, Johnson KA, O'Grady JP, Speroff L. Terbutaline and maternal cardiac function. JAMA 1981;246:2697–701*)

ANESTH ANALG
1982;61:473-4

Adverse Drug Interaction Involving Pancuronium and Aminophylline

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Aminophylline frequently is used as a bronchodilator in patients with reversible airway obstruction. Its use during anesthesia, however, is controversial (1). We describe a patient who was receiving therapeutic doses of aminophylline and who developed sudden supraventricular tachycardia following the administration of pancuronium.

Case Report

A 61-year-old, 83-kg, white man was scheduled to undergo lower thoracic posterior spinal fusion to stabilize a compression fracture of the 12th thoracic vertebra. Before the injury the patient had been in good health.

Six months before this admission, the patient had had a renal cyst drained under general anesthesia without complication. At that time, he reported a smoking history of 100 pack years. Pulmonary function tests demonstrated severe obstructive lung disease which responded to bronchodilators. Despite this, preoperative aminophylline was not given before or during that operation. The preoperative electrocardiogram (ECG) obtained during this admission showed that only infrequent premature atrial and ventricular beats and nonspecific ST-T changes. Blood gas tensions were normal. The anesthetic included preoperative diazepam (15 mg), Innovar, and thiopental for induction, followed by pancuronium, 8 mg, to facilitate tracheal intubation. Both surgery and anesthesia were well tolerated and no complications ensued.

During the present admission, because of his severe chronic obstructive pulmonary disease, the patient was given a loading dose of oral aminophylline (6 mg/kg), followed by 800 mg/day in divided doses for 1 week before surgery. Chest physiotherapy was also carried out. The patient had significant subjective improvement with this therapy. The serum aminophylline level on the 3rd day of treatment was 12.4 μg/ml. Chest roentgenogram was clear and ectopy was not present on an ECG taken the night before surgery. Other laboratory data were within normal limits.

On the morning of surgery, the patient received oral aminophylline (200 mg), and atropine (0.6 mg) and secobarbital (100 mg) intramuscularly. Forty-five minutes later, an ECG taken in the operating room revealed an occasional premature auricular contraction with sinus rate of 120 beats per minute. After he had breathed oxygen for 5 minutes, and after fentanyl, 150 μg, had been given intravenously, the heart rate decreased to 100 beats per minute. Thiopental, 300 mg, was then given, followed by pancuronium, 8 mg, when the eyelash reflex was obtunded. Approximately 3 minutes after the pancuronium had been given and while the patient was being ventilated with O_2, the heart rate suddenly increased to 180 beats per minute. ECG revealed the tachycardia to be supraventricular in origin. Arterial blood gas tensions and serum electrolyte levels at that time were pH 7.42, Pa_{CO_2} 38 torr, Pa_{O_2} 438 torr (F_{IO_2} 1.0), HCO_3^- 25 meq/L, Na^+ 142 meq/L, and K^+ 3.6 meq/L. Four successive intravenous doses of propranolol (0.25 mg) given over 10 minutes, and one intravenous dose of edrophonium, 15 mg, followed by left carotid sinus massage failed to affect the tachycardia. Anesthesia was deepened with additional thiopental (125 mg) but without slowing of heart rate. Up to this point, the patient's blood pressure remained stable (systolic 140 to 165 mm Hg, diastolic 100 to 110 mm Hg) and there was no wheezing. In view of the intractable tachycardia, it was considered unwise to proceed with the operation. The larynx was, therefore, intubated after application of topical lidocaine; and the patient was moved to the recovery room where mechanical ventilation was continued. Twenty minutes later, the tachycardia suddenly converted to normal sinus rhythm at a heart rate of 120 to 130 beats per minute. The aminophylline level at that time (8 hours after the last dose) was 8 μg/ml. Serum creatine phosphokinase (MB fraction) levels on three successive days thereafter were normal and a postoperative chest film in the recovery room was clear.

ECGs taken on subsequent days showed continued existence of atrial ectopy. As aminophylline provided subjective relief, the patient continued to take this medication after surgery. In view of the atrial ectopy he was digitalized before discharge and treated nonoperatively.

Discussion

It is our belief that the sudden provocation of supraventricular tachycardia soon after anesthetic induction represents a drug interaction between pancuronium and aminophylline. Several considerations support this viewpoint.

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First, the rather precise temporal relationship of the onset of the arrhythmia to the administration of pancuronium suggests that it was precipitated by pancuronium; there was no evidence of electrolyte or blood gas abnormality. Second, this patient had received pancuronium alone a few months previously without experiencing tachyarrhythmia. During the present anesthetic induction, the only alteration in management was the aminophylline regimen. Third, both aminophylline and pancuronium have adrenergic agonistic properties. Aminophylline inhibits phosphodiesterase (2) and stimulates catecholamine release from the adrenal medulla (3). It may also enhance the arrhythmogenic action of epinephrine by altering calcium accumulation within the sarcoplasmic reticulum (4). Pancuronium has been shown to inhibit the uptake of noradrenaline (5, 6), to exert an indirect sympathomimetic action (5, 7), and to possess strong vagolytic properties (8); it may also have an agonistic effect on beta-adrenoceptors (5). Pancuronium has been incriminated as the cause of severe intraoperative hypertension (9, 10).

In 1972, Levin and Dillon (11) recommended the use of pancuronium in the management of severe status asthmaticus; the four patients they described also received aminophylline. They did not provide information about the blood levels of aminophylline or about untoward hemodynamic changes that followed the administration of pancuronium. Soon after their paper was published, Beam (12) reported prolonged severe tachycardia after pancuronium was used in the management of status asthmaticus. In a recent study, Koehntop and associates (13) demonstrated that pharmacologic interference with intraneural norepinephrine uptake and phosphodiesterase inhibition can lead to a stepwise increase in arrhythmogenicity. This finding was substantiated recently by Edwards et al (14). Such a mechanism appears to be a reasonable explanation for the supraventricular tachycardia that complicated this case. Preexisting atrial ectopy and atropine premedication may have played a predisposing role in this adverse drug interaction between pancuronium and aminophylline.

It seems appropriate, therefore, to warn that the simultaneous administration of pancuronium and aminophylline may result in adverse arrhythmogenic effects. Preexisting heart disease (ectopy) may increase this potential.

ACKNOWLEDGMENTS

We thank J. C. Liao, MD, PhD for critically reviewing this case report, and Taunya C. Wegge and Nadine A. Beccue for their secretarial help in preparation of the manuscript.

REFERENCES

1. Stirt JA, Sullivan SF. Aminophylline. Anesth Analg 1981;60:587–602.
2. Butcher RW, Sutherland EW. Adenosine 3′,5′-phosphate in biologic materials. I. Purification and properties of cyclic 3′,5′-phosphate in human urine. J Biol Chem 1962;237:1244–50.
3. Poisner AM. Direct stimulant effect of aminophylline on catecholamine release from the adrenal medulla. Biochem Pharmacol 1973;22:469–73.
4. Johnson PN, Inesi C. Effect of methylxanthines and local anesthetics on fragmented sarcoplasmic reticulum. J Pharmacol Exp Ther 1969;169:308–14.
5. Docherty JR, McGrath JC. Sympathomimetic effects of pancuronium bromide on the cardiovascular system of the pithed rat: a comparison with the effect of drugs blocking the neuronal uptake of noradrenaline. Br J Pharmacol 1978;64:589–99.
6. Ivankovich AD, Miletich DJ, Albrecht RF, Lahed B. The effect of pancuronium on myocardial contraction and catecholamine metabolism. J Pharm Pharmacol 1975;27:837–41.
7. Domenech JS, Garcia RS, Sasiain JMR, Loyola AR, Oroz JS. Pancuronium bromide: an indirect sympathomimetic agent. Br J Anaesth 1976;48:1143–8.
8. Saxena PR, Bonta IL. Mechanisms of selective cardiac vagolytic action of pancuronium bromide: specific blockade of cardiac muscarinic receptors. Eur J Pharmacol 1970;11:332–41.
9. Fraley DS, Lemoncelli GL, Coleman A. Severe hypertension associated with pancuronium bromide. Anesth Analg 1978;57:265–7.
10. Jones RM, Hill AB. Severe hypertension associated with pancuronium in a patient with a phaeochromocytoma. Can Anaesth Soc J 1981;28:394–6.
11. Levin N, Dillon JB. Status asthmaticus and pancuronium bromide. JAMA 1972;222:1265–8.
12. Beam LR. Pancuronium bromide side effects. JAMA 1973;223:1265.
13. Koehntop DE, Liao JC, VanBergen FH. Effects of pharmacologic alterations of adrenergic mechanisms by cocaine, tropolone, aminophylline, and ketamine on epinephrine induced arrhythmias during halothane-nitrous oxide anesthesia. Anesthesiology 1977;46:83–93.
14. Edwards RP, Miller RD, Roizen MF, et al. Cardiac responses to imipramine and pancuronium during anesthesia with halothane or enflurane. Anesthesiology 1979;50:421–5.

letters TO THE EDITOR

Facial Paleness

To the Editor:

We recently encountered an unusual complication in a 58-year-old man having a coronary artery bypass procedure during which a bloodless pump prime was used. As cardiopulmonary bypass was initiated, a right-sided unilateral facial paleness, lasting approximately 60 seconds, was observed. The surgeons were notified and they thought the Sarns aortic cannula might be the cause. A thrill felt over the innominate artery disappeared when the cannula was repositioned. The patient had a left homonomous hemianopsia after surgery with no other neurologic problems.

It was felt that the aortic cannula had been placed in such a position that the pump flow was preferentially perfusing the right side of the head through the innominate artery and that the clear pump prime caused the transient paleness. This paleness cleared as the pump prime was then mixed with the patient's blood. Other possible causes of the neurologic sequelae could be emboli, hypoxia, or hypotension.

Gutman and Zeggra (1) at the Cleveland Clinic reviewed the ocular complications of cardiac surgery for both myocardial revascularization and valve replacement. In the 100 patients having myocardial revascularization, five developed ocular complications: three had homonomous hemianopsia and two had retinal infarcts. All five patients had an episode of either hypoxia, hypotension, or atrial fibrillation.

Ross et al (2) reported a case in which the left carotid artery was inadvertently cannulated during cardiopulmonary bypass for aortic valve replacement. There was low perfusion pressure during bypass and edema of the left side of the face together with rhinorrhea, otorrhea, and conjunctival edema. The patient developed neurologic, renal, and cardiovascular complications after surgery and died on the 5th postoperative day. Dalal and Patel (3) reported two cases of right-sided paleness with cardiopulmonary bypass attributed to carotid artery cannulation.

Our report indicates an unusual complication of open heart operations. It also emphasizes the necessity for continual observation of the patient and the operative field by the anesthesia team. Observation of the paleness in the case we have described and subsequent repositioning of the cannula by the surgeon, possibly adverted further neurologic damage in the patient.

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REFERENCES

1. Gutman FA, Zeggra H. Ocular complications in cardiac surgery. Surg Clin North Am 1971;51:1095–1103.
2. Ross WT, Lake CL, Wellons HA. Cardiopulmonary bypass complicated by inadvertent carotid cannulation. Anesthesiology 1981;54:85–86.
3. Dalal FY, Patel KD. Another sign of inadvertent carotid cannulation. Anesthesiology 1981;55:487.

* Reprint requests to Dr. Chapin.

Computer Programs for Acid-Base Variables

To the Editor:

I draw your attention to the interesting recent article by Gabel et al (1). This work is similar to the report by Jalowayski et al (2), published in 1968. The older program is also written in "Fortran IV" and also has the advantages of the "table-driven" technique described by Gabel et al. However, the older system will accept direct P_{O_2} input data and corrects for fetal hemoglobin oxygen saturation characteristics. It appears that most of the basic physiologic references in the older program are identical with those of the newer program. The older program also has the advantage of a tabular output for large groups of results in addition to the individual patient report format.

Having used the older program for a period of approximately 3 years with large numbers of samples, I can attest to its accuracy, simplicity, and usefulness. I can provide copies of the program to interested readers free of charge.

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REFERENCES

1. Gabel RA, Hooper A, Marseglia JJ Jr, Farese G. Calculation and correction of blood-gas and acid-base variables with a versatile computer program. Anesth Analg 1981;60:889–96.
2. Jalowayski A, Lauterbach R, Smith BE, Modell JH. A computer method for determinationof acid-base and oxygenation variables in adult and infant blood samples. J Lab Clin Med 1968;71:328–32.

To the Editor:

We are grateful to Dr. Smith for calling our attention to and sending us a copy of the program reported by Jalowayski et al in 1968 (1). Their program helps to illustrate the many advances in both blood-gas analysis and computer science that have occurred over the past 13 years. In the

late 1960s direct measurement of P_{CO_2} with the Severinghaus electrode was just replacing the Astrup technique, in which P_{CO_2} was estimated from three measurements of pH. P_{O_2} was still sometimes read from a pH meter (sic), requiring mathematical conversion to proper units. The program of Jalowayski et al (1) satisfied requirements of both the older and newer techniques of blood-gas analysis that were used in 1968.

Likewise, their program reflected conventional computer technology of the day. Data were punched onto cards and entered into the computer in batches, thus precluding interaction between the user and the computer. Only after peripheral terminals came into common use and after table-driven programming was developed in the early 1970s could users begin fashioning their own unique versions of generalized table-driven programs by interacting with the computer.

Our program, founded on innovative programming techniques, is designed to accommodate recent developments in measurement and interpretation of blood gases and pH. Because the science and technology of computers and of blood-gas analysis have changed so drastically since 1968, our program actually bears little resemblance to that of Jalowayski et al (1).

Many computer and calculator programs have been developed to assist in blood-gas analysis, some published before (2, 3) and others after (4-9) the work of Jalowayski et al. In our paper (10) we referred to the three programs that contributed most directly to our work (2, 8, 9). We enthusiastically acknowledge the substantial contributions of others to the field.

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REFERENCES

1. Jalowayski A, Lauterbach R, Smith BF, Modell JH. A computer method for determination of acid-base and oxygenation variables in adult and infant blood samples. J Lab Clin Med 1968;71:328-32.
2. Kelman GR. Digital computer subroutine for the conversion of oxygen tension into saturation. J Appl Physiol 1966;21:1375-6.
3. Dell RB, Engel K, Winters RW. A computer program for the blood pH-log P_{CO_2} nomogram. Scand J Clin Lab Invest 1967;19:29-37.
4. Vallbona C, Pevay E, McMath F. Computer analysis of blood gases and of acid-base status. Comput Biomed Res 1971;4:623-33.
5. Maas AHJ, Kreuger JA, Hoelen AJ, Visser BF. A computer program for calculating the acid-base parameters in samples of blood using a mini-computer. Pfluegers Arch 1972;334:264-75.
6. Hardt J. A computer program for calculating blood acid-base parameters on an Olivetti "Programma 101" desk computer. Clin Chem 1972;18:658-61.
7. Grogono W. Assessment of acid-base disturbances employing a desk-top computer. Br Med J 1973;1:381-6.
8. Gershwin R, Smith NT, Suwa K. An equation system and programs for obtaining base excess using a programmable calculator. Anesthesiology 1974;40:89-92.
9. Ruiz BC, Tucker WK, Kirby RR. A program for calculation of intrapulmonary shunts, blood-gas and acid-base values with a programmable calculator. Anesthesiology 1975;42:88-95.
10. Gabel RA, Hooper A, Marseglia JJ Jr, Farese G. Calculation and correction of blood-gas and acid-base variables with a versatile computer program. Anesth Analg 1981;60:889-96.

Modification of Dinamap 845 Automatic Blood Pressure Cuff to Permit Continuous Display of Cuff Pressure

To the Editor:

Use of the Dinamap 845 automatic blood pressure cuff in the operating room has become increasingly popular. A recent article (1) reported the possibility of barotrauma to the ulna nerve produced by malposition or prolonged inflation of the cuff. Venostasis manifested by petechiae, bluish discoloration, and edema of the extremity has also been observed (2).

Internal alarms to increase patient safety are a feature of the Dinamap. A red dot on the face of the device is illuminated when the exit valve is closed and pressure in the cuff exists. In addition, an alarm sounds if the cuff is inflated longer than 300 seconds. However, there is no provision for continuously reading cuff pressures during or between blood pressure determinations. Such a provision might aid in prevention of the complications noted with the use of the automatic cuff.

In order to observe cuff inflation pressures and to ensure deflation to zero pressure between determinations, we have devised a simple modification of the apparatus. A Y-piece is inserted into the tubing near the cuff. Two arms of the Y serve to pressurize the cuff and the third arm is connected by rubber tubing directly to the manometer on the anesthesia machine. This modification provides a continuous display of cuff pressure and, we feel, contributes to the safe use of this machine.

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REFERENCES

1. Sy WP. Ulna nerve palsy possibly related to use of automatically cycled blood pressure cuff. Anesth Analg 1981;60:687-8.
2. Showman A, Betts EK. Hazard of automatic noninvasive blood pressure monitoring. Anesthesiology 1981;55:717-8.

* Reprint requests to Dr. Glass.

Further Studies on the Myocardial Metabolic Effects of Protamine Sulfate following Cardiopulmonary Bypass

To the Editor:

The cardiovascular effects of rapid infusions of protamine have been described in man and appear to be benign (1). Recently, we described the effects of protamine on myocardial oxygen supply and demand in nine patients following cardiopulmonary bypass (2). Our results showed that there was no adverse alteration in the global myocardial metabolic state after rapid protamine infusion in

these patients. However, these patients formed a select group with good preoperative ventricular function, who did not require inotropic or vasoactive assistance at the conclusion of cardiopulmonary bypass.

In clinical practice, some patients do become unstable and require additional pharmacologic support at the time cardiopulmonary bypass is discontinued. The present report describes the myocardial metabolic effects of protamine infusion in 11 such patients [nine men, two women; mean age: 59 ± 9 (SD) years]. Before surgery, five patients had three-vessel, four patients had two-vessel, and two patients had single-vessel coronary artery disease. Preoperative left ventricular end-diastolic pressure (LVEDP) averaged 15 ± 7 mm Hg. Five patients were anesthetized with morphine sulfate (1 mg/kg IV), and six patients had halothane anesthesia (up to 2.5% halothane during induction, followed by maintenance of anesthesia with 0.5% to 1% halothane in oxygen). The mean ischemic time was 69 ± 29 minutes; the lowest body temperature during surgery was 20.6 ± 1.8°C. The average number of bypass grafts inserted was four. The mean total dose of heparin given to these patients was 263 ± 36 mg. At the time cardiopulmonary bypass was discontinued, seven patients required calcium chloride (mean dose: 1.1 g IV), two patients required phenylephrine (mean dose: 1.4 mg IV), and five patients required mephentermine (mean dose: 6.2 mg IV).

The methods used for this study, with their limitations, have been described previously (2). Control measurements were made when the patients were hemodynamically stable, which was a mean of 22 ± 11 minutes after administration of the vasoactive drug. Protamine was then infused (mean dose: 214 ± 47 mg over 5.5 ± 2.0 minutes), and measurements were repeated 10 minutes following protamine infusion. Hemodynamic data and myocardial metabolic measurements (mean ± SD) are shown in the Table. The control mean arterial pressure was 81 ± 10 mm Hg; the control mean cardiac index was 2.35 ± 0.69 L/min/m^2, with a mean pulmonary capillary wedge pressure of 15 ± 4 mm Hg. Protamine caused a significant reduction in cardiac index ($p <$ 0.01) which was due to a decrease in stroke volume index, as heart rate was unchanged. This reduction in stroke volume index, with no alteration in preload (pulmonary capillary wedge pressure) or afterload (systemic vascular resistance) suggests a direct myocardial depressant effect of protamine. No significant alterations were observed in any of the myocardial metabolic measurements. No patient developed electrocardiographic changes during the study. Two patients had perioperative myocardial infarctions as evidenced by serial ECG and enzyme changes.

TABLE

Cardiovascular Effect of Protamine Sulfate*

	Before protamine	After protamine
HR	82 ± 13	83 ± 13
MAP	81 ± 10	81 ± 9
PCWP	15 ± 4	14 ± 4
SVR	1459 ± 626	1678 ± 686
CI†	2.35 ± 0.69	2.04 ± 0.66
CBF	91 ± 26	84 ± 27
CS-O_2	6.0 ± 1.3	5.6 ± 0.7
MV_{O_2}	5.56 ± 2.1	5.42 ± 1.9
CS-lactate	2.61 ± 1.0	2.63 ± 1.0
RPP	9138 ± 1482	8770 ± 1827

* Values are means ± SD; N = 11. Abbreviations used are: HR, heart rate (beats/min); MAP, mean arterial pressure (mm Hg); PCWP, pulmonary capillary wedge pressure (mm Hg); SVR, systemic vascular resistance (dyne·sec·cm^{-5}); CI, cardiac index (L/min/m^2); CBF, coronary blood flow (ml/min); CS-O_2, coronary sinus oxygen content (ml O_2/dl); MV_{O_2}, myocardial oxygen consumption (ml/min); CS-lactate, coronary sinus lactate (mM/L); RPP, rate-pressure product.

† $p < 0.01$.

Although global lactate extraction and coronary sinus oxygen content did not change following protamine infusion in these patients, regional areas of metabolic deterioration may have been compensated for by improved metabolism elsewhere in the heart. Our study could not examine regional myocardial pathophysiology. Furthermore, we cannot rule out the contribution of the vasoactive medications to the hemodynamic and metabolic responses observed following protamine. Although our patients required pharmacologic support, they were hemodynamically stable at the time of the study. Based on our data, it appears that recent circulatory instability may be associated with a hemodynamic response to protamine different from that in a completely stable patient. The myocardial metabolic effects of rapid protamine infusion in patients who have greater circulatory instability or poor myocardial function are unknown.

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REFERENCES

1. Conahan TJ III, Andrews RW, McVaughn H III. Cardiovascular effects of protamine sulfate in man. Anesth Analg 1981;60:33–6.
2. Sethna DH, Moffitt E, Gray RJ, et al: Effects of protamine sulfate on myocardial oxygen supply and demand in patients following cardiopulmonary bypass. Anesth Analg 1982;61:247–51.

Indications for Pulmonary Arterial Catheterization

To the Editor:

Earlier, more unbridled enthusiasm (1) for pulmonary arterial (PA) catheterization of patients undergoing coronary artery revascularization has in recent years been tempered by the identification of potentially serious complications associated with the catheter's use (2), of potentially misleading "pit-falls" (3) in the interpretation of its data, and of subsets of patients having coronary arterial surgery less likely to demonstrate disparate ventricular function (4). Thus, the indications for PA catheterization have been modified to include principally those patients with more severely impaired left ventricular function (2).

An important implication of the investigation by Kaplan and Wells (5) is that perhaps we should (re-)expand the indications for PA catheter use, possibly to include all patients having coronary arterial surgery. Expanding their conclusions, one might argue

that if we cannot apply previously accepted criteria based on history, coronary arteriography, and left ventriculography in selecting before surgery, those patients likely to benefit from PA catheterization, and if subendocardial ischemia in a given patient may be missed if the catheter is not used, then should we not use the catheter in all patients having coronary arterial surgery? Not necessarily, because in fact, the conclusions of Kaplan and Wells are not supported by their findings.

First, the authors (5) argue that an elevated pulmonary capillary wedge pressure (PCWP) with abnormal wave forms is an indicator of (existing) myocardial ischemia. Although this may be a valid assumption for awake patients experiencing spontaneous and exercise-induced angina, it overlooks the effects of fluid loading with changes in intrapericardial pressure-volume relationships, and of halothane anesthesia, both of which can elevate PCWP in anesthetized patients without producing biochemical or ventriculographic evidence of myocardial ischemia. Second, the authors state that 55% of their patients demonstrated PCWP abnormalities as the only sign of ischemia. However, they also state that abnormal PCWP tracings were associated with significant elevations of central venous pressure. Moreover, their pressure tracings show marked increases in arterial blood pressure (BP)—from 110/60 mm Hg to approximately 165/105 mm Hg—occurring coincident with the PCWP abnormalities, and before electrocardiographic changes. Their table 2 (5) shows that in group I patients, elevated arterial blood pressure and abnormal ST-segments can occur in the absence of PCWP abnormalities. Thus, their data actually demonstrate that an elevated PCWP was never the only abnormality associated with ischemia! In fact, the data support the notion that hypertension is a better predictor of impending ischemia than is PCWP. Perhaps we might add another pitfall to PA catheterization: inadequate attention to other, less "glamorous" hemodynamic variables.

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REFERENCES

1. Swan HJC. CVP monitoring is outmoded, and of limited practical value. In: Inglefinger FJ, ed. Controversies in internal medicine—II. Philadelphia: WB Saunders, 1974:185–93.
2. Pace NL. A critique of flow-directed pulmonary arterial catheterization. Anesthesiology 1977;47:455–65.
3. Shin B, Ayella RJ, McAslan TC. Pitfalls of Swan-Ganz catheterization. Crit Care Med 1977;5:125–7.
4. Mangano DT. Monitoring pulmonary artery pressure in coronary-artery disease. Anesthesiology 1980;53:364–70.
5. Kaplan JA, Wells PH. Early diagnosis of myocardial ischemia using the pulmonary arterial catheter. Anesth Analg 1981;60:789–93.

To the Editor:

Once again Kaplan and Wells (1) have contributed to our understanding of the ischemic heart during anesthesia. What is a little disturbing is the diminutive role assigned to central venous pressure (CVP) in their discussion and conclusion. From the statistical data presented in their table 2 (1), the ischemic changes noted in groups II and III were associated with changes in CVP as well as pulmonary capillary wedge pressure (PCWP). Thus, according to their data a monitor of CVP would serve equally as well to detect episodes of myocardial ischemia without subjecting the patient to the added risk of pulmonary arterial catheterization.

The debate continues as to whether or not to catheterize the pulmonary artery (2). Mangano (3) has defined subgroups in which changes in CVP show little correlation with changes in PCWP, but the picture is far from clear (3). The morbidity and cost of routine pulmonary arterial catheterization must be evident to any department of anesthesia where these procedures are regularly performed. The debate is not served by the incomplete discussion and, I believe, misleading conclusion in the paper by Kaplan and Wells.

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REFERENCES

1. Kaplan JA, Wells PH. Early diagnosis of myocardial ischemia using the pulmonary arterial catheter. Anesth Analg 1981;60:789–93.
2. Lowenstein E, Teplick R: To (PA) catheterize or not to (PA) catheterize—that is the question (editorial). Anesthesiology 1980;361–3.
3. Mangano DT. Monitoring pulmonary arterial pressure in coronary-artery disease. Anesthesiology 1980;53:364–70.

To the Editor:

Lieberman has been a die-hard opponent of the use of the pulmonary arterial catheter (PAC) during coronary artery bypass graft (CABG) surgery since presenting an abstract entitled, "Wedge Pressure as a Predictor of Ischemia during CABG" in 1979 (the full text of his findings still remain unpublished) (1). His letter shows continued bias against hemodynamic monitoring, as well as a lack of understanding of the subtle changes occurring in the coronary circulation during CABG. More importantly, he missed the key point of our article, and failed to grasp the fact that group mean data do not necessarily represent the findings of an individual patient.

The indications for the use of a PAC during CABG are controversial and still evolving. The data of Mangano (2) on patients with poor left ventricular function (LVF) are widely accepted. However, his study revealed only the tip of the iceberg, as he compared only mean values of central venous pressure (CVP) and pulmonary capillary wedge pressure (PCWP) during periods when a mild elevation of left ventricular volume (Trendelenburg position) was the sole cardiovascular stress. Lowenstein and Teplick (3) pointed out in their accompanying editorial that increased afterload or contractility, or decreased oxygen supply, such as by coronary spasm, could markedly alter this relationship during CABG, even in patients with good LVF. In response to this editorial, we designed a prospective study to compare PCWP and CVP during CABG. It showed a very poor correlation between these pressures ($r = 0.59$) during the multiple stresses of CABG in 30 patients with good LVF (4).

The key point of our article was that the wave form of the PAC tracing should be observed, not just the level of the PCWP. It is the development of the large A and V waves that re-

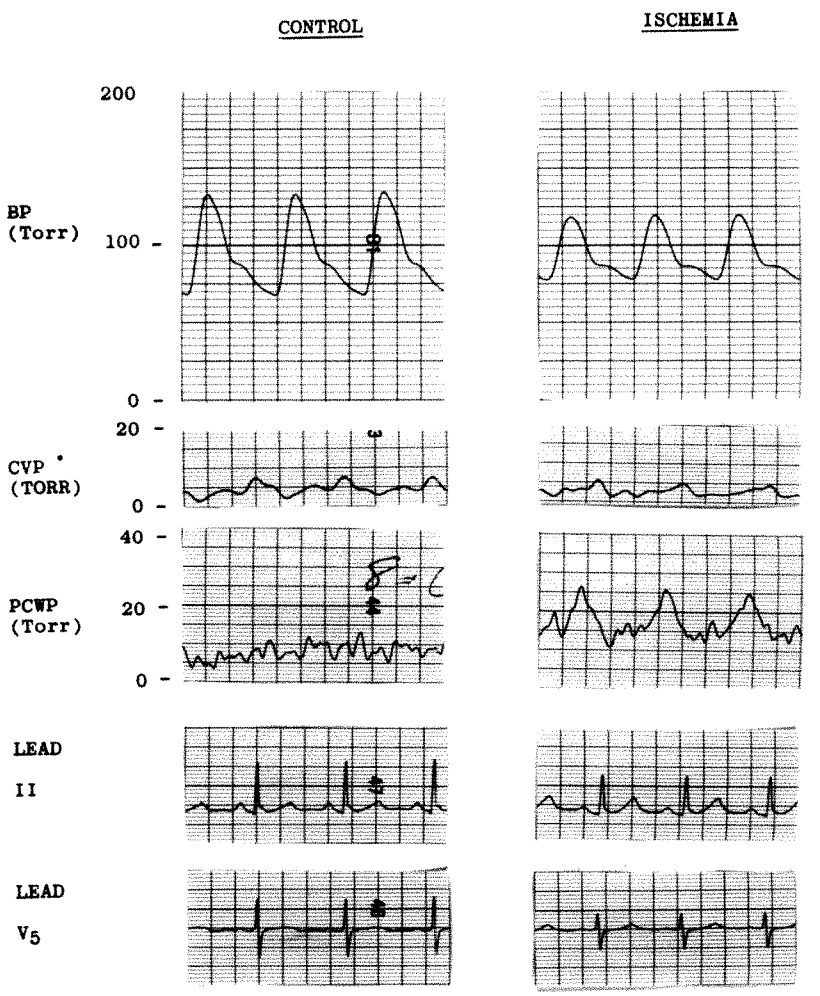


FIGURE. Hemodynamic data of one patient before and during myocardial ischemia. Decrease in left ventricular compliance (V wave) is seen as only early sign of ischemic episode.

flects the decrease in left ventricular compliance and/or papillary muscle insufficiency (mitral regurgitation) which can be produced by subendocardial ischemia. This is true in awake and anesthetized patients with ischemia, and does not occur in anesthetized patients with coronary artery disease given a fluid challenge or halothane, unless regional myocardial blood flow is compromised.

Noninvasive hemodynamic studies during anesthesia have demonstrated the occurrence of wall motion abnormalities and mitral regurgitation in patients with CABG before electrocardiographic (ECG) changes. These noninvasive findings correspond to the large A and V waves demonstrated by the PAC in our article. Elliot et al (5) showed mitral regurgitation by chest wall echocardiography; Barash et al (6) demonstrated a reduction in ejection fraction by nuclear scan.

Lieberman incorrectly states that "an elevated PCWP was never the only abnormality associated with ischemia," and Whalley worries about the diminutive role of the CVP. The Figure clearly shows the type pattern seen in some of the group III patients. The PCWP is increased and the V waves are 25 mm Hg, whereas the ECG is unchanged and the systemic blood pressure and CVP are actually decreased. The elevated PCWP with large V waves can be the earliest and the only sign of developing myocardial ischemia, as it was in this patient with good preoperative LVF. Therefore, the only "pitfall" is Lieberman's and Whalley's misinterpretation of the mean data for the group (e.g., CVP), as being representative of any individual patient. In some patients, the CVP increases along with the PCWP. However, the change in CVP is not as large in magnitude as that in the PCWP, and there are no changes in the wave form of the CVP in patients with acute subendocardial ischemia of the left ventricle.

The early changes of myocardial ischemia will be missed in many patients when only the ECG, blood pressure, and CVP are observed. Many patients with good LVF at rest, show changes in left ventricular compliance with stress [group IA of Waller and Kaplan (7)]. These patients can be identified by history (dyspnea as part of the symptom complex), nuclear stress tests, echocardiography, or an elevated left ventricular end-diastolic pressure after dye injection during cardiac catheterization. Clearly, these patients and others also require more sophisticated monitoring than the ECG for the detection of the early changes of myocardial ischemia. At the present time, this is best done clinically by comparing right and left ventricular filling pressures and wave forms.

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REFERENCES

1. Lieberman RW, Schwartz AJ, Jobes DR, Ominsky AJ, Andrews RW. Wedge pressure as a predictor of ischemia during CABG. Anesthesiology 1979;51:S59.
2. Mangano DT. Monitoring pulmonary arterial pressure in coronary-artery disease. Anesthesiology 1980;53:364-70.
3. Lowenstein E, Teplick R. To (PA) catheterize or not to (PA) catheterize—that is the question (editorial). Anesthesiology 1980;53: 361-3.
4. Waller JL, Johnson SP, Kaplan JA. Usefulness of pulmonary artery catheters during aortocoronary bypass surgery. Anesth Analg 1982;61:221-2.
5. Elliott PL, Schauble JF, Weiss J, Traill T, Flaherty J, O'Malley S. Echocardiography and LV function during anesthesia. Anesthesiology 1980;53:S105.
6. Barash PG, Kopriva CJ, Giles R, Jarabadkar S, Berger H, Zaret B. Global ventricular function and intubation: radionuclear profiles. Anesthesiology 1980;53:S109.
7. Waller JL, Kaplan JA. Anaesthesia for patients with coronary artery disease. Br J Anaesth 1981;53:757-67.

book REVIEWS

Narcotic Analgesics in Anesthesiology, edited by I. M. Kitahata and J. G. Collins, Baltimore, Williams & Wilkins Co., 1982, 259 pp, $34.00.

Narcotic Analgesics in Anesthesiology is a good book that fills a gap in the modern anesthesiologist's library. The book consists of 13 chapters with contributors primarily from the Departments of Anesthesiology, Neurosurgery, Obstetrics and Gynecology, and Medicine of Yale University School of Medicine, but also Carl Hug, MD, from the Department of Anesthesiology of Emory University. The text considers such various topics as: pharmacokinetics; endogenous opiate systems and opiate receptors; narcotic effects on the nervous system; narcotics and the circulation and respiratory systems; effects of narcotics on the gastrointestinal tract, liver, and kidneys; obstetric and neonatal implications of narcotic usage; narcotics for preoperative and postoperative medication; anesthetic care of the addicted patient; use of opioid analgesics in the treatment of chronic pain; and psychophysical studies of the effects of opioid analgesics on experimentally induced pain.

Although the book suffers to a small degree from the usual problems of a multiauthored text, i.e., duplication and variety of quality in the various chapters, it is an excellent reference for anesthesiologists, anesthesiology residents, medical students, and, to a certain extent, researchers involved in all the pharmacology and physiology of narcotic administration. Its primary orientation is toward the clinician, but its sophistication and breadth, especially in the chapter dealing with pharmacokinetics but also in some of the other chapters, makes it a valuable text for virtually any biologist interested in narcotic compounds. The chapters are presented in a logical sequence, and the material is easy to read.

Although the reader may disagree with some of the opinions of the authors, in general, the material presented can be considered to be the state-of-the-art in 1982. The book should be in the library of all anesthetic departments, as well as in the libraries of all residents, physicians, and nurses involved in anesthesiology.

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Ethics and Regulation of Clinical Research, by R. J. Levine, Baltimore, Urban & Schwarzenberg, 1981, 299 pp, $35.00.

I approached the review of this book with something less than full enthusiasm, wondering whether the subject matter was particularly relevant to anesthesiologists. This feeling abated somewhat when I noted the author had dedicated his work to the late Dr. Henry K. Beecher, Professor of Anesthesia at Harvard Medical School and an historical figure in the area of medical ethics, and to Dr. Franz Ingelfinger, a former editor of *The New England Journal of Medicine*.

No pretense is made that this work is encyclopedic because, as Levine points out, more than 4000 articles have been published on the subject of informed consent alone. The first three chapters introduce concepts and terminology pertaining to human research, information that may be unfamiliar to those not dealing regularly with this subject matter. The historical development of the Department of Health and Human Services, the Declaration of Helsinki, the Nuremberg Code, and the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research are traced in some detail, as is the evolution of hospital and medical school institutional review boards.

I personally found the middle chapters of the book to be most interesting and informative. Topics covered include subject selection; informed consent (the longest chapter and perhaps of most interest to the anesthesiologist as the subject is compared with and contrasted to informed consent for medical treatment); deception; and research on the mentally infirm, institutionalized patients, children, prisoners, and the fetus.

Numerous "facts" are presented throughout, but this book is not simply a compendium of rules and regulations pertaining to human research. Rather, it is a sensitive revelation of an obviously dedicated scientist's attempt to bring rationality and reason into an area often controlled by emotion and little else. Some topics are fascinating. For example, because of the problems concerning research in children, in 1975 more than 80% of the drugs prescribed for children had not been approved for such use, and this fact was so stated in the labeling of these med-

ications. A class of "therapeutic orphans" resulted. Although the Federal Drug Administration has stated that labeling is not intended "either to preclude the physician from using his best judgement in the interest of the patient, or to impose liability if he does not follow the package insert," some courts have held that the package insert is prima facie evidence of the standard of due care. Thus, the physician using these drugs in children may be subject to malpractice litigation.

Who should read this book? Probably all institutional review board members, many of whom I suspect have no clear idea of their board's historic development or change, and certainly all basic or clinical scientists who delve into human research, as well as those who control it. As Levine states, "a competent clinical researcher need never have heard of Doctors Sydenbam, Bichat, Bernard, Osler, or even Beecher, not to mention Aristotle, Immanuel Kant, Talcott Parsons or Benjamin Cardozo. But there are those who are pleased that they have."

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Chest Physiotherapy in the Intensive Care Unit, by C. F. Mackenzie, N. Ciesla, P. C. Imle, and N. Klemic, Baltimore, Williams & Wilkins Co., 1981, 260 pp, $23.00.

This text succeeds in providing an in-depth description of chest physical therapy services provided at the Maryland Institute for Emergency Medical Service Systems. All aspects of such therapy are amply covered including a review of respiratory anatomy; the indications, precautions, and contraindications of therapy; and physiologic alterations during and following therapy. Excellent discussions pertaining to specific patient populations such as spinal cord injuries and pediatrics are included.

If any weakness exists in this text, it lies within the limitation of the patient population discussed. The vast majority of patients in the authors' institution are men between the ages of 16 and 30 years. Therefore, the information given in the text generally pertains to young, previously healthy, traumatized patients. This limits the usefulness of the text with regard to elderly and chronically diseased medical patients. The authors purposely make no attempt to relate the therapies as carried out in their institution to other accepted treatment regimens popularized in other patient populations.

The text is well written and the illustrations and chest radiograms add greatly to its instructional value. We feel this book is of benefit to all professionals concerned with the respiratory aspects of critically ill patients even though it deals exclusively with physical therapy modalities as applied to the respiratory care patient.

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BOOKS RECEIVED

Handbook of Critical Care, Second Edition, edited by J. L. Berk and J. E. Sampliner, Boston, Little, Brown and Co, 1982, 688 pp, $24.50.

Cardiac Anesthesia, by T. J. Conahan, Menlo Park, CA, Addison-Wesley Publishing Co, Inc, 1982, 340 pp, $29.95.

Respiratory Failure in the Child, edited by G. A. Gregory, New York, Churchill Livingstone, Inc, 1981, 205 pp, $32.50.

Obstetric Anesthesia: The Complicated Patient, by F. M. James and A. S. Wheeler, Philadelphia, FA Davis Co, 1982, 346 pp, $40.00.

Persistent Pain: Modern Methods of Treatment, Volume 3, edited by S. Lipton and J. Miles. New York, Grune & Stratton, 1981, 260 pp, $48.00.

A Guide for Authors

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References. (The following style will appear in the journal effective volume 60, January 1981.) Number references consecutively in the order in which they are first mentioned in the text. Identify references in text, tables, and legends by arabic numerals (in parentheses). References cited *only* in tables or in legends to figures should be numbered in accordance with a sequence established by the first identification in the text of the particular table or illustration.

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Avoid abstracts as references; "unpublished observations" and "personal communications" may not be used as references, although references to written, not verbal, communications may be inserted (in parentheses) in the text. Include among the references manuscripts accepted but not yet published; designate the journal followed by "in press" (in parentheses). Information from manuscripts submitted but not yet accepted should be cited in the text as "unpublished observations" (in parentheses).

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Examples of correct forms:

Journal

1. Standard Journal Article (List all authors when six or less; when seven or more, list only first three and add et al)

   Soter NA, Wasserman SI, Austen KF. Cold urticaria: release into the circulation of histamine and eosinophil chemotactic factor of anaphylaxis during cold challenge. N Engl J Med 1976;294:687-90.

2. Corporate Author

   The Committee on Enzymes of the Scandinavian Society for Clinical Chemistry and Clinical Physiology. Recommended method for the determination of gamma-glutamyltransferase in blood. Scand J Clin Lab Invest 1976;36:119-25.

   Anonymous. Epidemiology for primary health care. Int J Epidemiol 1976;5:224-5.

Books and Other Monographs

3. Personal Author(s)

   Osler AG. Complement: mechanisms and functions. Englewood Cliffs: Prentice-Hall, 1976.

4. Corporate Author

   American Medical Association Department of Drugs. AMA drug evaluations. 3rd ed. Littleton: Publishing Sciences Group, 1977.

5. Editor, Compiler, Chairman as Author

   Rhodes AJ, Van Rooyen CE, comps. Textbook of virology: for students and practitioners of medicine and the other health sciences. 5th ed. Baltimore: Williams & Wilkins, 1968.

6. Chapter in Book

   Weinstein L, Swartz MN. Pathogenic properties of invading microorganisms. In: Sodeman WA Jr, Sodeman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: WB Saunders, 1974:457-72.

7. Agency Publication

   National Center for Health Statistics. Acute conditions: incidence and associated disability, United States July 1968-June 1969. Rockville, Md.: National Center for Health Statistics, 1972. (Vital and health statistics. Series 10: Data from the National Health Survey, no. 69) (DHEW publication no. (HSM)72-1036).

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Omit internal horizontal and vertical rules.

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The editor on accepting a manuscript may recommend that additional tables containing important backup data too extensive to be published may be deposited with the National Auxiliary Publications Service or made available by the author(s). In that event, an appropriate statement will be added to the text. Submit such table for consideration with the manuscript.

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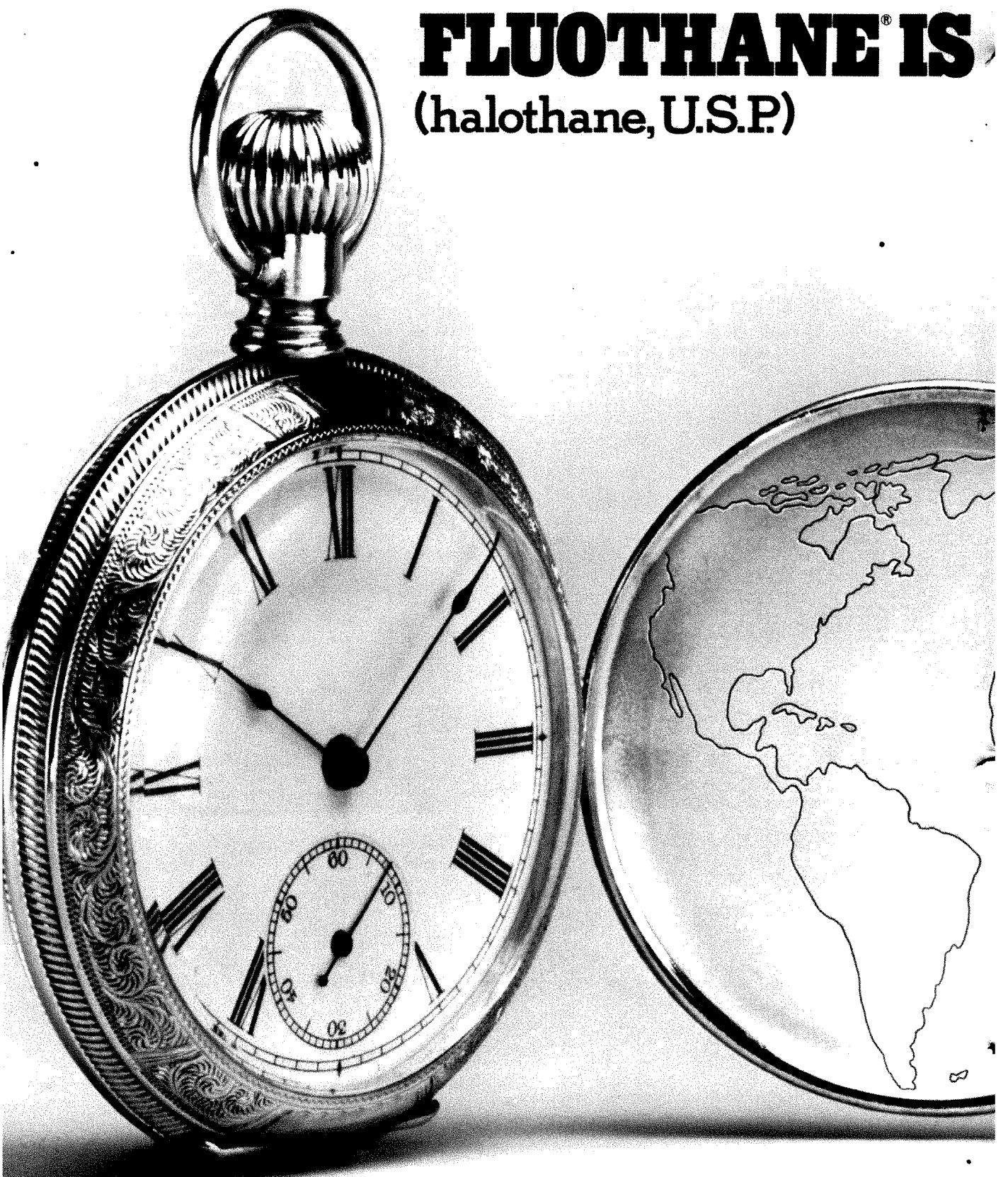
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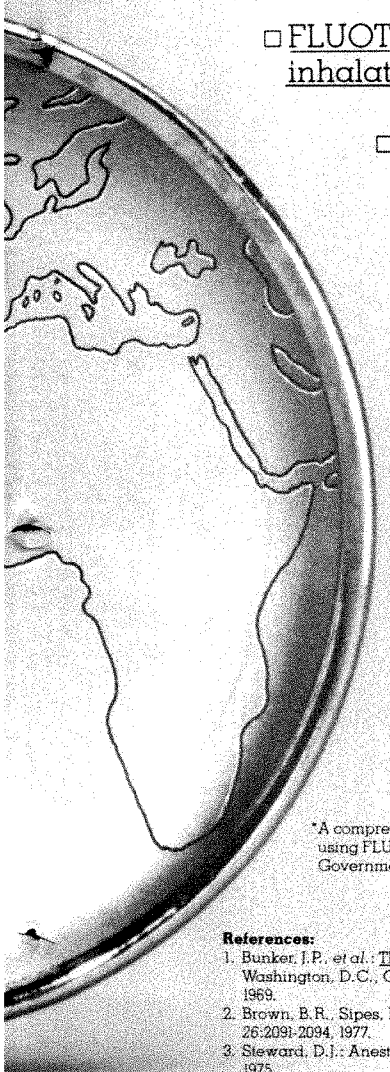
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*A comprehensive retrospective analysis covering 856,000 general anesthesias—nearly one-third using FLUOTHANE. Bunker, J.P., *et al.*: The National Halothane Study. Washington, D.C., Government Printing Office, 1969.

References:

1. Bunker, J.P., *et al.*: The National Halothane Study. Washington, D.C., Government Printing Office, 1969.
2. Brown, B.R., Sipes, I.G.: Biochem. Pharmacol. 26:2091-2094, 1977.
3. Steward, D.J.: Anesthesiology 43:268-276 (Aug.) 1975.
4. Proceedings, Virginia Society of Anesthesiologists, April 20-22, 1979, Richmond, VA.

See following page for Brief Summary.

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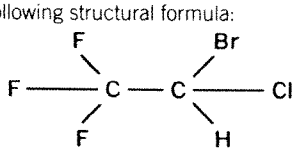
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(Complete text of package circular.)

Description. FLUOTHANE, brand of halothane, U.S.P., is an inhalation anesthetic. It is 2-bromo-2-chloro-1, 1, 1-trifluoroethane and has the following structural formula:



The specific gravity is 1.872-1.877 at 20°C, and the boiling point (range) is 49°C – 51°C at 760 mm Hg. The vapor pressure is 243 mm Hg at 20°C. The blood/gas coefficient is 2.5 at 37°C, and the olive oil/water coefficient is 220 at 37°C. Vapor concentrations within anesthetic range are nonirritating and have a pleasant odor. FLUOTHANE is nonflammable, and its vapors mixed with oxygen in proportions from 0.5 to 50 per cent (v/v) are not explosive.

FLUOTHANE does not decompose in contact with warm soda lime. When moisture is present, the vapor attacks aluminum, brass, and lead, but not copper. Rubber, some plastics, and similar materials are soluble in FLUOTHANE; such materials will deteriorate rapidly in contact with FLUOTHANE vapor or liquid. Stability of FLUOTHANE is maintained by the addition of 0.01 per cent thymol (w/w), up to 0.00025% ammonia (w/w), and storage is in amber colored bottles.

FLUOTHANE should not be kept indefinitely in vaporizer bottles not specifically designed for its use. Thymol does not volatilize along with FLUOTHANE, and therefore accumulates in the vaporizer, and may, in time, impart a yellow color to the remaining liquid or to wicks in vaporizers. The development of such discoloration may be used as an indicator that the vaporizer should be drained and cleaned, and the discolored FLUOTHANE (halothane, U.S.P.) discarded. Accumulation of thymol may be removed by washing with diethyl ether. After cleaning a wick or vaporizer, make certain all diethyl ether has been removed before reusing the equipment to avoid introducing ether into the system.

Actions. FLUOTHANE is an inhalation anesthetic. Induction and recovery are rapid and depth of anesthesia can be rapidly altered. FLUOTHANE progressively depresses respiration. There may be tachypnea with reduced tidal volume and alveolar ventilation. FLUOTHANE is not an irritant to the respiratory tract, and no increase in salivary or bronchial secretions ordinarily occurs. Pharyngeal and laryngeal reflexes are rapidly obtunded. It causes bronchodilation. Hypoxia, acidosis, or apnea may develop during deep anesthesia.

FLUOTHANE reduces the blood pressure, and frequently decreases the pulse rate. The greater the concentration of the drug, the more evident these changes become. Atropine may reverse the bradycardia. FLUOTHANE does not cause the release of catecholamines from adrenergic stores. FLUOTHANE also causes dilation of the vessels of the skin and skeletal muscles.

Cardiac arrhythmias may occur during FLUOTHANE anesthesia. These include nodal rhythm, AV dissociation, ventricular extrasystoles and asystole. FLUOTHANE sensitizes the myocardial conduction system to the action of epinephrine and norepinephrine, and the combination may cause serious cardiac arrhythmias. FLUOTHANE increases cerebral spinal fluid pressure. FLUOTHANE produces moderate muscular relaxation. Muscle relaxants are used as adjuncts in order to maintain lighter levels of anesthesia. FLUOTHANE augments the action of nondepolarizing relaxants and ganglionic blocking agents. FLUOTHANE is a potent uterine relaxant.

Indications. FLUOTHANE (halothane, U.S.P.) is indicated for the induction and maintenance of general anesthesia.

Contraindications. FLUOTHANE is not recommended for obstetrical anesthesia except when uterine relaxation is required.

Warnings. When previous exposure to FLUOTHANE was followed by unexplained jaundice, consideration should be given to the use of other agents.

FLUOTHANE should be used in vaporizers that permit a reasonable approximation of output, and preferably of the calibrated type. The vaporizer should be placed out of circuit in closed circuit rebreathing systems; otherwise overdosage is difficult to avoid. The patient should be closely observed for signs of overdosage, *i.e.*, depression of blood pressure, pulse rate, and ventilation, particularly during assisted or controlled ventilation.

Usage in Pregnancy. Safe use of FLUOTHANE has not been established with respect to possible adverse effects upon fetal development. Therefore, FLUOTHANE should not be used in women where pregnancy is possible and particularly during early pregnancy, unless, in the judgment of the physician, the potential benefits outweigh the unknown hazards to the fetus.

Precautions. The uterine relaxation obtained with FLUOTHANE, unless carefully controlled, may fail to respond to ergot derivatives and oxytocic posterior pituitary extract.

FLUOTHANE increases cerebrospinal fluid pressure. Therefore, in patients with markedly raised intracranial pressure, if FLUOTHANE is indicated, administration should be preceded by measures ordinarily used to reduce cerebrospinal fluid pressure. Ventilation should be carefully assessed, and it may be necessary to assist or control ventilation to insure adequate oxygenation and carbon dioxide removal.

Epinephrine or norepinephrine should be employed cautiously, if at all, during FLUOTHANE (halothane, U.S.P.) anesthesia since their simultaneous use may induce ventricular tachycardia or fibrillation.

Nondepolarizing relaxants and ganglionic blocking agents should be administered cautiously, since their actions are augmented by FLUOTHANE.

It has been reported that in genetically susceptible individuals, the use of general anesthetics and the muscle relaxant, succinylcholine, may trigger a syndrome known as malignant hyperthermic crisis. Monitoring temperature during surgery will aid in early recognition of this syndrome. Dantrolene sodium and supportive measures are generally indicated in the management of malignant hyperthermia.

Adverse Reactions. The following adverse reactions have been reported: mild, moderate and severe hepatic dysfunction (including hepatic necrosis), cardiac arrest, hypotension, respiratory arrest, cardiac arrhythmias, hyperpyrexia, shivering, nausea, and emesis.

Dosage and Administration. FLUOTHANE may be administered by the nonrebreathing technic, partial rebreathing, or closed technic. The induction dose varies from patient to patient. The maintenance dose varies from 0.5 per cent to 1.5 per cent.

FLUOTHANE may be administered with either oxygen or a mixture of oxygen and nitrous oxide.

How Supplied. No. 3125—Unit packages of 125 ml and 250 ml of halothane, U.S.P., stabilized with 0.01% thymol (w/w), and up to 0.00025% ammonia (w/w). 7197/R82

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The Bronx-Lebanon Hospital Center is seeking application and nominations for the position of Director for the Department of Anesthesiology. The candidate must have broad experience in the clinical practice of anesthesiology, a demonstrated proficiency in administration, and experience in teaching.

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References: 1. Gyermek L: *Curr Ther Res* 18:377-386, 1975. **2.** Katz RL: *Anesthesiology* 28:528-534, 1967.

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When used as an antagonist to nondepolarizing muscle relaxants, adequate recovery of voluntary respiration and neuromuscular transmission must be obtained prior to discontinuation of respiratory assistance and there should be continuous patient observation. Satisfactory recovery may be defined by a combination of clinical judgement, respiratory measurements and observation of the effects of peripheral nerve stimulation. If there is any doubt concerning the adequacy of recovery from the effects of the nondepolarizing muscle relaxant, artificial ventilation should be continued until all doubt has been removed.

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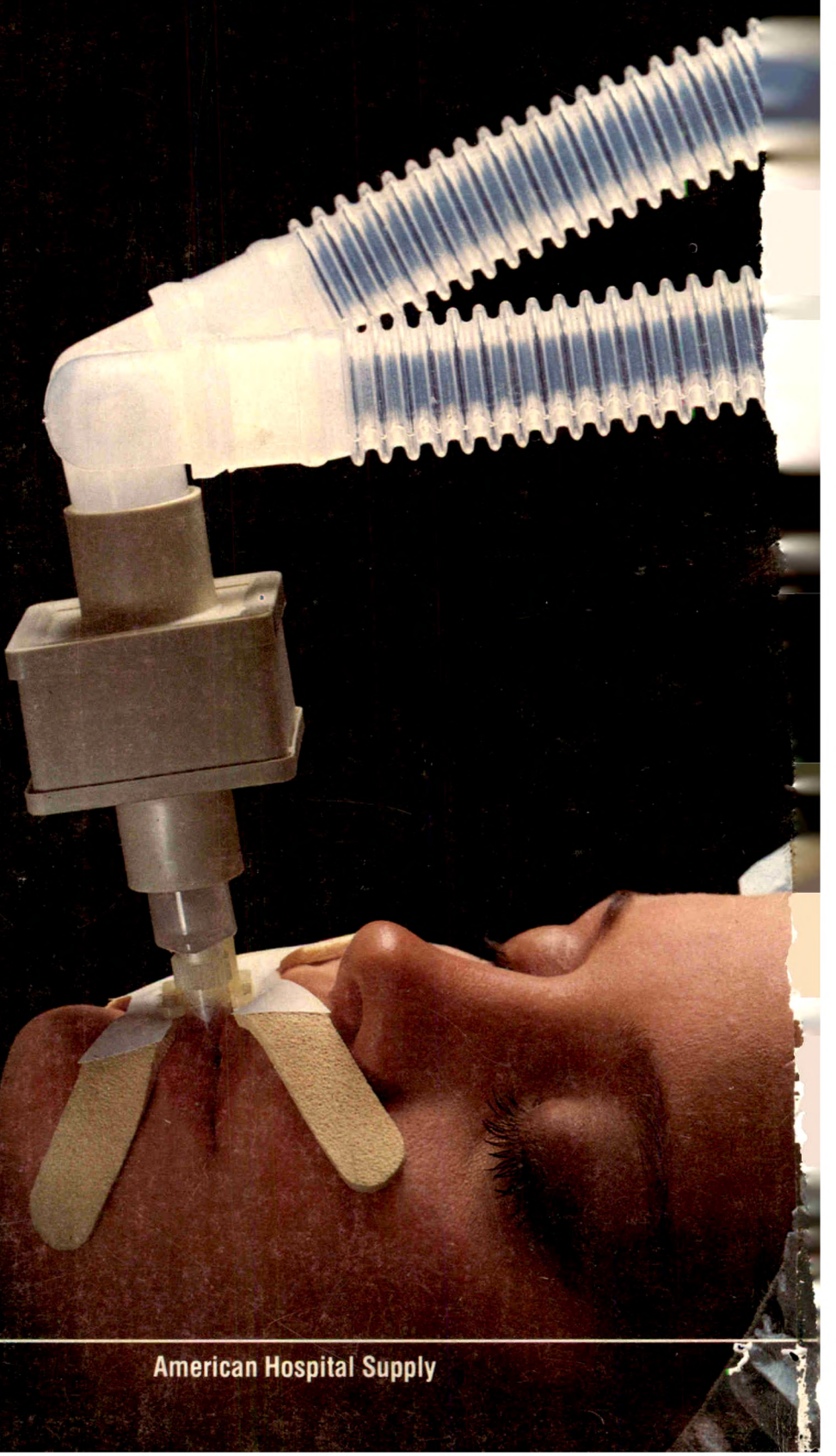
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